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NEWS	7	FEB 06	Patent sequence location (PSL) data added to USGENE
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NEWS	12	FEB 23	Several formats for image display and print options discontinued in USPATFULL and USPAT2
NEWS	13	FEB 23	MEDLINE now offers more precise author group fields and 2009 MeSH terms
NEWS	14	FEB 23	TOXCENTER updates mirror those of MEDLINE - more precise author group fields and 2009 MeSH terms
NEWS	15	FEB 23	Three million new patent records blast AEROSPACE into STN patent clusters
NEWS	16	FEB 25	USGENE enhanced with patent family and legal status display data from INPADOCDB
NEWS	17	MAR 06	INPADOCDB and INPAFAMDB enhanced with new display formats
NEWS	18	MAR 11	EPFULL backfile enhanced with additional full-text applications and grants
NEWS	19	MAR 11	ESBIOBASE reloaded and enhanced
NEWS	20	MAR 20	CAS databases on STN enhanced with new super role for nanomaterial substances
NEWS	21	MAR 23	CA/Caplus enhanced with more than 250,000 patent equivalents from China
NEWS	22	MAR 30	IMSPATENTS reloaded and enhanced
NEWS	23	APR 03	CAS coverage of exemplified prophetic substances enhanced
NEWS	24	APR 07	STN is raising the limits on saved answers

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=> file caplus medline

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FULL ESTIMATED COST	0.22	0.22

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FILE 'MEDLINE' ENTERED AT 13:55:17 ON 11 APR 2009

=> s (?isothiocyanate) and (cancer or tumor or neoplasm)

L1 4609 (?ISOTHIOCYANATE) AND (CANCER OR TUMOR OR NEOPLASM)

=> s l1 and ?cysteine

L2 231 L1 AND ?CYSTEINE

=> s l2 and lun

L3 0 L2 AND LUN

=> s l3 and lung

L4 0 L3 AND LUNG

=> s l2 and lung

L5 52 L2 AND LUNG

=> dup rem l5

PROCESSING COMPLETED FOR L5

L6 34 DUP REM L5 (18 DUPLICATES REMOVED)

=> d l6 ibib abs 1-34

L6 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:286210 CAPLUS

DOCUMENT NUMBER: 148:315348

TITLE: Salts of benzimidazolyl pyridyl ethers and formulations thereof for cancer treatment

INVENTOR(S): Gullapalli, Rampurna; Hashash, Ahmad; Karpinski, Piotr H.; Lin, Kangwen L.; Loeser, Eric M.; Okhamafe, Augustus O.; Sutton, Paul Allen; Sy, Eduardo

PATENT ASSIGNEE(S): Novartis AG, Switz.

SOURCE: PCT Int. Appl., 65pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008027523	A2	20080306	WO 2007-US19152	20070830
WO 2008027523	A3	20080410		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2007290388	A1	20080306	AU 2007-290388	20070830
PRIORITY APPLN. INFO.:			US 2006-841177P	P 20060830
			US 2007-954466P	P 20070807
			WO 2007-US19152	W 20070830

AB Salts of benzimidazolyl pyridyl ethers are provided, particularly salts of [1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzimidazol-2-yl]-(4-trifluoromethyl-phenyl)amine (I). Compns. and formulations including such salts and surfactants as well as methods of preparing such compns. and formulations for treatment of various cancers are described. Thus, the compound of Formula I was prepared and converted to various salt forms via an acid-base reaction in an organic liquid medium followed by a slow evaporation of the organic solvent or by precipitation from the organic solvent in case of mesylate, esylate, and maleate salts. The salts obtained were formulated in oral dosage forms, i.e., capsules and tablets. For example, 400 mg of granules obtained by wet granulation of I 12.5, methanesulfonic acid 9.5, Crospovidone 20.0, Poloxamer 188 10.0, and microcryst. cellulose 48% were mixed with sodium starch glycolate 20 mg, silica 10 mg, and magnesium stearate 10 mg and filled into a gelatin capsule.

L6 ANSWER 2 OF 34 MEDLINE on STN
ACCESSION NUMBER: 2008130918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18156316
TITLE: Combined effects of sulindac and suberoylanilide hydroxamic acid on apoptosis induction in human lung cancer cells.
AUTHOR: Seo Sung-Keum; Jin Hyeon-Ok; Lee Hyung-Chahn; Woo Sang-Hyeok; Kim Eun-Sung; Yoo Doo-Hyun; Lee Su-Jae; An Sungkwan; Rhee Chang-Hun; Hong Seok-Il; Choe Tae-Boo; Park In-Chul
CORPORATE SOURCE: Laboratory of Radiation Resistance Control, Korea Institute of Radiological and Medical Sciences, 215-4 Gongneung-Dong, 139-706 Nowon-Ku, Seoul, Korea.
SOURCE: Molecular pharmacology, (2008 Mar) Vol. 73, No. 3, pp. 1005-12. Electronic Publication: 2007-12-21. Journal code: 0035623. E-ISSN: 1521-0111.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200804

ENTRY DATE: Entered STN: 23 Feb 2008
Last Updated on STN: 8 Apr 2008
Entered Medline: 7 Apr 2008

AB Histone deacetylase (HDAC) inhibitors represent a promising group of anticancer agents. Treatment of cancer cells with HDAC blockers, such as suberoylanilide hydroxamic acid (SAHA), leads to the activation of apoptosis-promoting genes. To enhance proapoptotic efficiency, SAHA has been used in conjunction with radiation, kinase inhibitors, and cytotoxic drugs. In the present study, we show that at the suboptimal dose of 250 μ M, sulindac [2-[6-fluoro-2-methyl-3-[(4-methylsulfinylphenyl)methylidene]inden-1-yl]-acetic acid] significantly enhances SAHA-induced growth suppression and apoptosis of A549 human non-small cell lung cancer cells, primarily via enhanced collapse of the mitochondrial membrane potential, release of cytochrome c, and caspase activation. Furthermore, sulindac/SAHA cotreatment induced marked down-regulation of survivin at both the mRNA and protein levels and stimulated the production of reactive oxygen species (ROS), which were blocked by the antioxidant N-acetyl-l-cysteine. Overexpression of survivin was associated with reduced sulindac/SAHA-induced apoptosis of A549 cells, whereas suppression of survivin levels with antisense oligonucleotides or small interfering RNA further sensitized cells to sulindac/SAHA-induced cell death. Our results collectively demonstrate that sulindac/SAHA-induced apoptosis is mediated by ROS-dependent down-regulation of survivin in lung cancer cells.

L6 ANSWER 3 OF 34 MEDLINE on STN
ACCESSION NUMBER: 2008738781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 19003576
TITLE: Binding to protein by isothiocyanates: a potential mechanism for apoptosis induction in human non small lung cancer cells.
AUTHOR: Mi Lixin; Chung Fung-Lung
CORPORATE SOURCE: Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA.
CONTRACT NUMBER: R01 AT003623 (United States NCCAM NIH HHS)
SOURCE: Nutrition and cancer, (2008) Vol. 60 Suppl 1, pp. 12-20. Journal code: 7905040. E-ISSN: 1532-7914.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200902
ENTRY DATE: Entered STN: 15 Nov 2008
Last Updated on STN: 15 Feb 2009
Entered Medline: 12 Feb 2009

AB The upstream events by which isothiocyanates (ITCs) induce apoptosis have not been fully investigated. Numerous studies have reported that the apoptosis was induced by ITCs through generation of reactive oxygen species (ROS) as a result of conjugating with and, consequently, depleting cellular glutathione. As electrophiles, ITCs could potentially trigger apoptosis by binding to macromolecules including DNA and proteins. The results showed that DNA damage may not be an important early event for the apoptosis induction by ITCs. Phenethyl isothiocyanate (PEITC) is a more potent inducer of apoptosis than sulforaphane (SFN) in A549 cells, but SFN induces more ROS generation and oxidative damages than PEITC, suggesting that oxidative stress again is probably not a trigger for apoptosis in these cells. In contrast, we found that PEITC binds more to intracellular proteins than SFN. We identified tubulin as 1 of the protein targets of ITCs through proteomics approach. We showed that the relative tubulin binding affinity of ITCs correlates well with their

potency of cell growth inhibition and apoptosis induction. These results collectively suggest that the covalent binding to protein targets, such as tubulin, by ITCs is an important chemical event in apoptosis induction by ITCs in human lung A549 cells.

L6 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:34293 CAPLUS
DOCUMENT NUMBER: 146:135598
TITLE: Nrf2-based compositions and methods for the treatment or prevention of disorders relating to oxidative stress
INVENTOR(S): Biswal, Shyam; Dore, Sylvain; Thimmulappa, Rajesh Kumar; Rangasamy, Tirumalai; Sakata, Yoshihito; Shah, Zahoor Ahmad; Zhuang, Hean; Singh, Anju
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 249pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007005879	A2	20070111	WO 2006-US26056	20060703
WO 2007005879	A3	20080612		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2006265113	A1	20070111	AU 2006-265113	20060703
CA 2614110	A1	20070111	CA 2006-2614110	20060703
EP 1959969	A2	20080827	EP 2006-799996	20060703
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS			

PRIORITY APPLN. INFO.:
US 2005-696485P P 20050701
US 2006-800975P P 20060517
WO 2006-US26056 W 20060703

AB The invention discloses methods for treating or preventing conditions, diseases, or disorders related to oxidative stress. In one embodiment, the method increases Nrf2 biol. activity or expression. In particular, the invention provides for the treatment or prevention of diseases relating to oxidative stress including emphysema, sepsis, septic shock, ischemic injury, cerebral ischemia and neurodegenerative disorders, meningitis, encephalitis, hemorrhage, cerebral ischemia, heart ischemia, cognitive deficits and neurodegenerative disorders.

L6 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2007:748971 CAPLUS
DOCUMENT NUMBER: 147:109217
TITLE: The Role of Protein Binding in Induction of Apoptosis by Phenethyl Isothiocyanate and Sulforaphane in Human Non-Small Lung Cancer

AUTHOR(S): Cells
 Mi, Lixin; Wang, Xiantao; Govind, Sudha; Hood, Brian
 L.; Veenstra, Timothy D.; Conrads, Thomas P.; Saha,
 Daniel T.; Goldman, Radoslav; Chung, Fung-Lung
 CORPORATE SOURCE: Department of Oncology, Lombardi Comprehensive Cancer
 Center, Georgetown University, Washington, DC, USA
 SOURCE: Cancer Research (2007), 67(13), 6409-6416
 CODEN: CNREA8; ISSN: 0008-5472
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Induction of apoptosis underlies a mechanism for inhibiting tumorigenesis
 by phenethyl isothiocyanate (PEITC) and sulforaphane (SFN).
 However, the upstream events by which isothiocyanates (ITC) induce
 apoptosis have not been fully investigated. As electrophiles, ITCs could
 trigger apoptosis by binding to DNA or proteins or by inducing oxidative
 stress. To better understand the mol. mechanisms of apoptosis by ITCs, we
 examined, as a first step, the role of these events in human non-small
 lung cancer A549 cells. PEITC was a more potent inducer
 than SFN; it induced apoptosis at 20 $\mu\text{mol/L}$, whereas SFN induced at 40
 $\mu\text{mol/L}$ but not at 20 $\mu\text{mol/L}$. To study binding with cellular
 proteins and DNA, cells were treated with ^{14}C -ITCs; the initial protein
 binding by PEITC was almost 3-fold than that of SFN. The binding by PEITC
 increased with time, whereas binding by SFN remained low. Therefore, 4 h
 after incubation proteins became the predominant targets for PEITC with a
 6-fold binding than that of SFN. To characterize the chemical nature of
 binding by the ITCs, we used bovine serum albumin (BSA) as a surrogate
 protein. PEITC also modified BSA covalently to a greater extent than SFN
 occurring exclusively at cysteine residues. Surprisingly,
 neither PEITC nor SFN bound to DNA or RNA at detectable levels or caused
 significant DNA strand breakage. The levels of oxidative damage in cells,
 measured as reactive oxygen species, 8-oxo-deoxyguanosine, and protein
 carbonyls formation, were greater in cells treated with SFN than PEITC.
 Because PEITC is a stronger inducer of apoptosis than SFN, these results
 indicate that direct covalent binding to cellular proteins is an important
 early event in the induction of apoptosis by the ITCs.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 34 MEDLINE on STN
 ACCESSION NUMBER: 2007283707 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 17491244
 TITLE: [Genotype-disease association and possibility to reveal
 environmentally modifiable disease causes: the use of
 mendelian randomization principle].
 Asociace genotypu s nemoci a odhalovani jejich prostredim
 ovlivnitelnych pricin: vyuziti principu mendelovske
 randomizace.
 AUTHOR: Novotny L; Bencko V
 CORPORATE SOURCE: Ustav hygieny a epidemiologie 1, LF UK a VFN, Praha..
 lnovo@lf1.cuni.cz
 SOURCE: Casopis lekar u c eskyh, (2007) Vol. 146, No. 4, pp.
 343-50.
 Journal code: 0004743. ISSN: 0008-7335.
 PUB. COUNTRY: Czech Republic
 DOCUMENT TYPE: (ENGLISH ABSTRACT)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: Czech
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200706
 ENTRY DATE: Entered STN: 15 May 2007
 Last Updated on STN: 23 Jun 2007

Entered Medline: 22 Jun 2007

AB Though the methodology and designs of epidemiological studies and analyses of medical databases have improved, associations between modifiable exposures and the disease in observational epidemiological studies remain partly biased. Mendelian randomization principle, which is the random distribution of parental genes to offspring in meiosis during gametogenesis and at conception, represents a chance for methodology of evaluation of the causal relations between the external cause and the disease. The use of this principle assumes the association between the disease and the genetic polymorphism which reflects the biological relation between the suspected exposure and the disease, and is generally less prone to the phenomenon of confounding and reverse causation that can impair the interpretation of results in conventional observational studies. Authors describe explanatory options of the Mendelian randomization principle using examples in folic acid--homocysteine--coronary heart disease, and isothiocyanate versus lung carcinoma. Though the use of Mendelian randomization principle has its limitations, it offers new possibilities to test causal relations and clearly shows that means invested into the Human genome project can contribute to the understanding and prevention of adverse effects of modifiable exposure to the human health.

L6 ANSWER 7 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2006:318526 CAPLUS

DOCUMENT NUMBER: 144:344946

TITLE: Molecular toxicity models based on gene expression profiles in isolated rat hepatocytes exposed to known hepatotoxins

INVENTOR(S): Higgs, Brandon; Elashoff, Michael; Mendrick, Donna L.; Porter, Mark W.; Castle, Arthur L.; Johnson, Kory R.

PATENT ASSIGNEE(S): Gene Logic, Inc., USA

SOURCE: PCT Int. Appl., 271 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2006037025	A2	20060406	WO 2005-US34780	20050928
WO 2006037025	A3	20060713		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

PRIORITY APPLN. INFO.: US 2004-613292P P 20040928

AB The present invention includes methods of predicting hepatotoxicity of test agents and methods of generating hepatotoxicity prediction models using algorithms for analyzing quant. gene expression information. Isolated Sprague-Dawley rat hepatocytes exposed to known hepatotoxins were examined to identify changes in genes expression induced by these compds. using the Affymetrix Rat Microarray. These changes in gene expression provide useful toxicity markers than can be used to monitor toxicity

and/or toxicity progression by a test compound. Some of these markers may also be used to monitor or detect various disease or physiologic states, disease progression, drug efficacy, and drug metabolism. The invention also includes microarrays, computer systems comprising the toxicity prediction models, as well as methods of using the computer systems by remote users for determining the toxicity of test agents.

L6 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2006:369635 CAPLUS
DOCUMENT NUMBER: 145:55909
TITLE: Natural or synthesized phenethyl
isothiocyanate and its metabolite used in
treatment of cancer
INVENTOR(S): Wang, Longgui; Qiao, Renwei; Cheng, Jingcai
PATENT ASSIGNEE(S): Wuxi Jiexi Medical Science and Technology Co., Ltd.,
Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 22 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
CN 1724516	A	20060125	CN 2005-10040865	20050630
PRIORITY APPLN. INFO.:			CN 2005-10040865	20050630

AB The invention discloses a natural or synthesized isothiocyanate and its in vivo metabolite, which are represented by corresponding formulas in the claims. The inventive isothiocyanate is capable of inhibiting both DNA methylation and histone deacetylase (HADC), thereby resuming the expression of some important genes in cancer cell, which have been shut down abnormally. The invention also provides the use of the isothiocyanate in the treatment of malignant tumors, including leukemia and solid tumors.

L6 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2006:307919 CAPLUS
DOCUMENT NUMBER: 144:406256
TITLE: Early Loss of Fhit in the Respiratory Tract of Rodents
Exposed to Environmental Cigarette Smoke
AUTHOR(S): D'Agostini, Francesco; Izzotti, Alberto; Balansky,
Roumen; Zanesi, Nicola; Croce, Carlo M.; De Flora,
Silvio
CORPORATE SOURCE: Department of Health Sciences, University of Genoa,
Genoa, I-16132, Italy
SOURCE: Cancer Research (2006), 66(7), 3936-3941
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Fhit gene, encompassing the most active common human chromosomal fragile region, FRA3B, has been shown to act as a tumor suppressor. Several studies have shown significant Fhit alterations or Fhit protein loss in lung cancers from smokers compared with lung cancers from nonsmokers. To evaluate the role of Fhit under controlled experimental conditions, we exposed rodents to environmental cigarette smoke (ECS) and evaluated Fhit expression or Fhit protein in the respiratory tract. After 14 days of exposure to ECS, loss of Fhit protein in the bronchial/bronchiolar epithelium affected half of the tested B6-129(F1) mice, either wild type or Fhit+/- . After 28 days, it affected the vast majority of the tested

SKH-1 hairless mice and of A/J mice and all (UL53-3 x A/J)F1 mice, either wild type or P53+/- . In Sprague-Dawley rats, exposure to ECS for up to 30 days caused a time-dependent loss of Fhit in pulmonary alveolar macrophages. Moreover, ECS down-regulated Fhit expression and significantly decreased Fhit protein in the rat bronchial epithelium. The oral administration of N-acetylcysteine attenuated the ECS-related loss of Fhit, whereas oltipraz, 5,6-benzoflavone, phenethyl isothiocyanate, and indole 3-carbinol, and their combinations had no significant effect. Parallel studies evaluated a variety of mol., biochem., and cytogenetic alterations in the respiratory tract of the same animals. In conclusion, there is unequivocal evidence that Fhit is an early, critical target in smoke-related lung carcinogenesis in rodents, and that certain chemopreventive agents can attenuate the occurrence of this gene alteration.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2005:1002398 CAPLUS

DOCUMENT NUMBER: 143:401016

TITLE: Phenethyl Isothiocyanate and Sulforaphane
and their N-Acetylcysteine Conjugates
Inhibit Malignant Progression of Lung
Adenomas Induced by Tobacco Carcinogens in A/J Mice
AUTHOR(S): Conaway, C. Clifford; Wang, Chung-Xiou; Pittman,
Brian; Yang, Yang-Ming; Schwartz, Joel E.; Tian, Defa;
McIntee, Edward J.; Hecht, Stephen S.; Chung,
Fung-Lung

CORPORATE SOURCE: American Health Foundation Cancer Center, Institute
for Cancer Prevention, Valhalla, NY, USA

SOURCE: Cancer Research (2005), 65(18), 8548-8557
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 143:401016

AB We have shown previously that naturally occurring isothiocyanates derived from cruciferous vegetables and their N-acetylcysteine conjugates inhibit lung adenoma formation induced by tobacco carcinogens in A/J mice at the post-initiation stage. The tumor-inhibitory activity by these compds. is linked with activation of activator protein and induction of apoptosis in lung tissues, suggesting that these compds. may also inhibit the development of adenomas to adenocarcinomas in lung. In this study, the chemopreventive activity of phenethyl isothiocyanate and sulforaphane and their N-acetylcysteine conjugates during progression of lung adenomas to malignant tumors was investigated in A/J mice. Mice were divided into 14 groups and treated with a mixture of 3 μ mol benzo(a)pyrene [B(a)P] and 3 μ mol 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) given by gavage once weekly for 8 wk. Twenty weeks after the beginning of carcinogen administration, a total of 20 mice in the treatment groups were sacrificed with an average yield of 7.3 \pm 4.5 lung adenomas per mouse. The remaining mice in each group were fed diets containing phenethyl isothiocyanate (3 and 1.5 mmol/kg diet), sulforaphane (3 and 1.5 mmol/kg diet), phenethyl isothiocyanate-N-acetylcysteine (8 and 4 mmol/kg diet), sulforaphane-N-acetylcysteine (8 and 4 mmol/kg diet) during weeks 21 to 42. Four mice in each of the high-dose treatment groups were sacrificed during weeks 28 and 36 and the bioassay was terminated during week 42; lung tissues were harvested for histopathol. examination of tumors and for cell proliferation (proliferating cell nuclear antigen) and apoptosis (caspase-3) assays

using immunohistochem. staining. At termination, the incidence of adenocarcinoma in the 3 mmol/kg diet phenethyl isothiocyanate group and 8 mmol/kg diet phenethyl isothiocyanate-N-acetylcysteine group was reduced to 19% and 13%, resp., compared with 42% in the carcinogen-treated control group. At the lower doses, phenethyl isothiocyanate and its N-acetylcysteine conjugate also inhibited the incidences of lung adenocarcinoma, however, the decreases were not statistically significant. The lung tumor incidences in groups treated with sulforaphane-N-acetylcysteine in the diet were also significantly reduced to 11% or 16%. Furthermore, the malignant lung tumor multiplicity was significantly reduced from 1.0 tumor/mouse in the carcinogen-treated control group to 0.3 in the sulforaphane low-dose group, 0.3 and 0.4 in the two sulforaphane-N-acetylcysteine groups, and 0.4 in the phenethyl isothiocyanate high-dose group. The malignant tumor multiplicities in other treatment groups were also reduced (0.5-0.8 tumors/mouse), but not significantly. Unlike lung adenocarcinomas, both incidences and multiplicities of lung adenomas were not much affected by treatment with isothiocyanates or their conjugates. Immunohistochem. examination of the lung tumors from all time points indicated that significant reduction in proliferating cell nuclear antigen and induction of apoptosis (terminal nucleotidyl transferase-mediated nick end labeling and caspase-3) were observed in the isothiocyanate and isothiocyanate-N-acetylcysteine-treated groups that showed inhibition of the development of lung adenocarcinomas. The results of the study provide a basis for future evaluation of the potential of phenethyl isothiocyanate and sulforaphane and their conjugates as chemopreventive agents in smokers and ex-smokers with early lung lesions.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2005:1002397 CAPLUS

DOCUMENT NUMBER: 143:259787

TITLE: N-Acetylcysteine Conjugate of Phenethyl Isothiocyanate Enhances Apoptosis in Growth-Stimulated Human Lung Cells

AUTHOR(S): Yang, Yang-Ming; Jhanwar-Uniyal, Meena; Schwartz, Joel; Conaway, C. Clifford; Halicka, H. Dorota; Traganos, Frank; Chung, Fung-Lung

CORPORATE SOURCE: Divisions of Carcinogenesis and Molecular Epidemiology, American Health Foundation Cancer Center, Institute for Cancer Prevention, Valhalla and Brander Cancer Research Institute, New York Medical College, Hawthorne, NY, USA

SOURCE: Cancer Research (2005), 65(18), 8538-8547
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors previously showed that dietary treatment with the N-acetylcysteine conjugate of phenethyl isothiocyanate (PEITC-NAC) inhibited benzo(a)pyrene-induced lung tumorigenesis in A/J mice, and that tumor inhibition was associated with induction of activator protein-1 (AP-1) activity and stimulation of apoptosis in the lungs of mice. In the present study, the authors show that PEITC-NAC also induces apoptosis and AP-1 activity in human lung adenocarcinoma A549 cells, and that activation of AP-1 is important in PEITC-NAC induced apoptosis in these cells.

PEITC-NAC induced AP-1 binding activity in A549 cells in a dose- and time-dependent manner; peak activity appeared at 10 $\mu\text{mol/L}$ after 24 h. At that time, flow cytometric anal. showed a sub-G1 peak, indicating that .apprx.4.5% of the cells had undergone apoptosis. When wild-type c-jun cDNA was transfected into A549 cells, PEITC-NAC-mediated apoptosis was greatly increased in the c-jun-transfected cells compared with the control vector-transfected cells, based on cell morphol. and anal. of DNA fragmentation. Furthermore, cells that were pretreated with 100 nmol/L 12-O-tetradecanoyl phorbol-13-acetate, and then treated with 25 $\mu\text{mol/L}$ PEITC-NAC, underwent enhanced apoptosis compared with cells that were treated with PEITC-NAC alone; cells treated with 12-O-tetradecanoyl phorbol-13-acetate alone showed active cell growth without apoptosis. Bivariate flow cytometric anal. of DNA strand breaks vs. DNA content showed that apoptosis induced by PEITC-NAC occurred predominantly in the G2-M phase. These findings suggest that growth-stimulated cells with an elevated basal AP-1 activity, i.e., A549 cells transfected with wild-type c-jun or treated with a tumor promoter, were more sensitive to PEITC-NAC-mediated apoptosis. The observation that PEITC-NAC induces apoptosis predominantly in growth-promoted cells, such as neoplastic cells, suggests a selective mechanism by which PEITC-NAC inhibits lung carcinogenesis.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2005:1254919 CAPLUS

DOCUMENT NUMBER: 144:16674

TITLE: Modulation of multigene expression and proteome profiles by chemopreventive agents

AUTHOR(S): Izzotti, Alberto; Bagnasco, Maria; Cartiglia, Cristina; Longobardi, Mariagrazia; Camoirano, Anna; Tampa, Elena; Lubet, Ronald A.; De Flora, Silvio

CORPORATE SOURCE: Department of Health Sciences, University of Genoa, Genoa, I-16132, Italy

SOURCE: Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis (2005), 591(1-2), 212-223
CODEN: MUREAV; ISSN: 0027-5107

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Anal. of transcriptome and proteome profiles by microarray technologies provides a formidable, new tool in cancer chemoprevention research. An ideal chemopreventive agent should not excessively alter per se the basal make-up of multigene expression and protein synthesis and should at the same time be able to attenuate alterations induced by risk factors. In order to validate this working hypothesis, the authors previously performed a series of studies in animal models using the thiol N-acetyl-L-cysteine (NAC) and the nonsteroidal anti-inflammatory drug sulindac. The authors report herein the results of new studies evaluating modulation of DNA adduct levels and expression of 4858 genes in lung and liver of Sprague-Dawley rats, either unexposed or exposed to environmental cigarette smoke (ECS). The tested chemopreventive agents included NAC, oltipraz (OPZ), 5,6-benzoflavone (5,6-BF), phenethyl isothiocyanate (PEITC), and indole 3-carbinol (I3C). Combinations of OPZ with NAC and of PEITC with I3C were also assayed. Excepting OPZ, all treatments inhibited by at least 50% the formation of bulky DNA adducts in the lung of ECS-exposed rats. Hierarchical cluster anal. and principal component anal. allowed us to classify the agents according to their influence on basal gene expression and their ability to attenuate ECS-induced transcriptome alterations. PEITC and I3C were the most effective but the least safe agents. 5,6-BF displayed intermediate patterns. OPZ was poorly effective in lung and considerably

altered the basal gene expression in liver. NAC had a medium efficacy and was the safest agent, as also supported by the anal. of 518 proteins in rat lung.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2005:1254916 CAPLUS
DOCUMENT NUMBER: 144:16342
TITLE: Modulation of apoptosis by cancer chemopreventive agents
AUTHOR(S): D'Agostini, Francesco; Izzotti, Alberto; Balansky, Roumen M.; Bennicelli, Carlo; De Flora, Silvio
CORPORATE SOURCE: Department of Health Sciences, University of Genoa, Genoa, I-16132, Italy
SOURCE: Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis (2005), 591(1-2), 173-186
CODEN: MUREAV; ISSN: 0027-5107
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, of almost 2000 studies showed that the large majority of 39 putative cancer chemopreventive agents induced "spontaneous" apoptosis. Inhibition of the programmed cell death triggered by a variety of stimuli was consistently reported only with ascorbic acid, α -tocopherol, and N- acetylcysteine (NAC). We performed exptl. studies in rodents exposed to cigarette smoke, either mainstream (MCS) or environmental (ECS), and UV-A/B-containing light. The nonsteroidal anti-inflammatory drug sulindac did not affect the apoptotic process in the skin of light-exposed mice and in the lungs of ECS-exposed mice. Likewise, 5,6-benzoflavone, indole-3-carbinol, 1,2-dithiole-3-thione and oltipraz failed to modulate apoptosis in the respiratory tract of ECS-exposed rats. Phenethyl isothiocyanate further enhanced the frequency of apoptosis in pulmonary alveolar macrophages and bronchial epithelial cells, and upregulated several genes in the lung of ECS-exposed rats. Both individually and in combination with oltipraz, NAC inhibited apoptosis in the respiratory tract of rats exposed either to MCS or ECS. Moreover, NAC attenuated the ECS-related overexpression of proapoptotic genes and normalized the levels of proapoptotic proteins in rat lung. The transplacental administration of NAC to mice considerably attenuated gene overexpression in the liver of fetuses exposed to ECS throughout pregnancy. Inhibition of apoptosis by chemopreventive agents reflects their ability to counteract certain upstream signals, such as genotoxic damage, redox imbalances, and other forms of cellular stress that trigger apoptosis. On the other hand, enhancement of apoptosis is a double-edged sword, since it represents a protective mechanism in carcinogenesis but may contribute to the pathogenesis of other degenerative diseases. We suggest that stimulation of apoptosis by so many chemopreventive agents, as reported in the literature, may often reflect the occurrence of toxic effects at high doses.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:589413 CAPLUS
DOCUMENT NUMBER: 141:134062
TITLE: Compositions and methods for treating lung cancer
INVENTOR(S): Chung, Fung-Lung; Conaway, C. Clifford; Yang, Yang-Ming
PATENT ASSIGNEE(S): American Health Foundation, USA

SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004060365	A1	20040722	WO 2003-US41785	20031230
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003300171	A1	20040729	AU 2003-300171	20031230
US 20060241178	A1	20061026	US 2006-541256	20060417
PRIORITY APPLN. INFO.:			US 2002-437240P	P 20021230
			WO 2003-US41785	W 20031230

AB The invention is directed to methods and compns. of inhibiting lung tumorigenesis. Such method involves the administration of an isothiocyanate conjugate at the post-initiation stage of tumor growth, while avoiding the drawbacks of toxicity of the parent compds.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
 ACCESSION NUMBER: 2003:875277 CAPLUS
 DOCUMENT NUMBER: 139:364833
 TITLE: Preparation of heterocyclic thiol compounds as matrix metalloprotease inhibitors
 INVENTOR(S): Kajino, Masahiro; Takizawa, Masayuki; Notoya, Kohei; Nara, Hiroshi; Ikemoto, Tomomi; Nishiguchi, Atsuko
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 116 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091242	A1	20031106	WO 2003-JP5255	20030424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2483515	A1	20031106	CA 2003-2483515	20030424
AU 2003235121	A1	20031110	AU 2003-235121	20030424

the most dramatic catastrophes of the 20th century. The control of this plague is one of the major challenges of preventive medicine for the next decades. The imperative goal is to refrain from smoking. However, chemoprevention by dietary and/or pharmacol. agents provides a complementary strategy, which can be targeted not only to current smokers but also to former smokers and passive smokers. This article summarizes the results of studies performed in the authors' labs. during the last 10 yr, and provides new data generated in vitro, in exptl. animals and in humans. The authors compared the ability of 63 putative chemopreventive agents to inhibit the bacterial mutagenicity of mainstream cigarette smoke. Modulation by ethanol and the mechanisms involved were also investigated both in vitro and in vivo. Several studies evaluated the effects of dietary chemopreventive agents towards smoke-related intermediate biomarkers in various cells, tissues and organs of rodents. The investigated end-points included metabolic parameters, adducts to Hb, bulky adducts to nuclear DNA, oxidative DNA damage, adducts to mitochondrial DNA, apoptosis, cytogenetic damage in alveolar macrophages, bone marrow and peripheral blood erythrocytes, proliferation markers, and histopathol. alterations. The agents tested in vivo included N-acetyl-l-cysteine, 1,2-dithiole-3-thione, oltipraz, phenethyl isothiocyanate, 5,6-benzoflavone, and sulindac. The authors started applying multigene expression anal. to chemoprevention research, and postulated that an optimal agent should not excessively alter per se the physiol. background of gene expression but should be able to attenuate the alterations produced by cigarette smoke or other carcinogens. The authors are working to develop an animal model for the induction of lung tumors following exposure to cigarette smoke. The most encouraging results were so far obtained in models using A/J mice and Swiss albino mice. The same smoke-related biomarkers used in animal studies can conveniently be applied to human chemoprevention studies. The authors participated in trials evaluating the effects of N-acetyl-l-cysteine and oltipraz in smokers from Italy, The Netherlands, and the People's Republic of China. The authors are trying to develop a pharmacogenomic approach, e.g. based on genetic metabolic polymorphisms, aimed at predicting not only the risk of developing cancer but also the individual responsiveness to chemopreventive agents.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 2002:666445 CAPLUS

DOCUMENT NUMBER: 138:265227

TITLE: Inhibition of lung tumorigenesis in A/J mice by N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-cysteine and myo-inositol, individually and in combination

AUTHOR(S): Hecht, Stephen S.; Upadhyaya, Pramod; Wang, Mingyao; Bliss, Robin L.; McIntee, Edward J.; Kenney, Patrick M. J.

CORPORATE SOURCE: University of Minnesota Cancer Center, Minneapolis, MN, 55455, USA

SOURCE: Carcinogenesis (2002), 23(9), 1455-1461
CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Isothiocyanates, their N-acetylcysteine conjugates, and myo-inositol (MI) are inhibitors of lung tumorigenesis in A/J mice. However, chemoprevention by combinations of these compds. in different temporal sequences has not been examined This is important for developing practical approaches to lung cancer chemoprevention in smokers and ex-smokers. We used a tumor

model in which A/J mice are treated with 8 weekly doses of benzo[a]pyrene (B[a]P) plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and killed 19 wk after the final treatment. In Experiment 1, isothiocyanates or their N-acetylcysteine conjugates were added to the diet (1 or 3 $\mu\text{mol/g}$) from 1 wk before until 1 wk after carcinogen treatment. The compds. were 2-phenethyl isothiocyanate (PEITC), 3-phenylpropyl isothiocyanate (PPITC), N-acetyl-S-(N-benzylthiocarbamoyl)-L-cysteine (BITC-NAC), N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-cysteine (PEITC-NAC), and N-acetyl-S-(N-3-phenylpropylthiocarbamoyl)-L-cysteine (PPITC-NAC). Significant redns. in lung tumor multiplicity were observed in mice treated with PEITC, PEITC-NAC, PPITC and PPITC-NAC. PEITC-NAC was chosen for combination studies with MI (Experiment 2). Mice were treated with B[a]P plus NNK without or with PEITC-NAC (3 $\mu\text{mol/g}$ diet), MI (55.5 $\mu\text{mol/g}$ diet), or PEITC-NAC plus MI (3 μmol plus 55.5 $\mu\text{mol/g}$ diet). Different temporal sequences of dietary addns. were investigated: carcinogen treatment phase; post-carcinogen treatment phase; entire experiment; 50% of carcinogen treatment phase until termination; and 75% of carcinogen treatment phase until termination. All treatments reduced lung tumor multiplicity except PEITC-NAC post-carcinogen or from 75% of the carcinogen treatment phase. Reduction of lung tumor multiplicity by PEITC-NAC plus MI was greater than that in the mice treated with the agents alone in all temporal sequences. When all results were combined, PEITC-NAC plus MI was significantly more effective than the agents alone. There was a significant trend for reduction in lung tumor multiplicity with increased duration of treatment by the chemopreventive agents. These results provide a basis for further development of mixts. of PEITC-NAC and MI for chemoprevention of lung cancer.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 2002:205671 CAPLUS

DOCUMENT NUMBER: 137:57131

TITLE: Expression of cyclin D1/2 in the lungs of strain A/J mice fed chemopreventive agents

AUTHOR(S): Witschi, Hanspeter; Espiritu, Imelda; Suffia, Marie; Pinkerton, Kent E.

CORPORATE SOURCE: Center for Health and the Environment and Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, 95616, USA

SOURCE: Carcinogenesis (2002), 23(2), 289-294

CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Male strain A mice were fed a diet containing chemopreventive agents. After 1 and 3 wk on the diets, lung nuclear fractions were examined for expression of cyclin D1/2 with western blot anal. In animals fed a diet containing a mixture of myoinositol and dexamethasone, a treatment found previously to be effective in preventing the development of tobacco smoke-induced lung tumors in A/J mice, cyclin D1/2 expression was reduced to 30-40% of control levels. A similar decrease in cyclin D1/2 expression was found when animals were fed either myoinositol or dexamethasone alone. Paradoxically, tobacco smoke by itself had a similar effect on cyclin D1/2 expression. On the other hand, several agents that had been previously found not to be effective against tobacco smoke carcinogenesis [phenethyl isothiocyanate, 1,4-phenylenebis(methylene)selenoisocyanate, N-acetylcysteine, acetylsalicylic acid, D-limonene and beta carotene] did not decrease

cyclin D1/2 expression after 1 or 3 wk of feeding. It was concluded that expression of cyclin D1/2 might be a potentially useful marker in the identification of chemopreventive agents for tobacco smoke and could be of some help in the evaluation of their effects.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2002:70893 CAPLUS

DOCUMENT NUMBER: 136:262469

TITLE: Inhibition of benzo(a)pyrene-induced lung tumorigenesis in A/J mice by dietary N-acetylcysteine conjugates of benzyl and phenethyl isothiocyanates during the postinitiation phase is associated with activation of mitogen-activated protein kinases and p53 activity and induction of apoptosis

AUTHOR(S): Yang, Yang-Ming; Conaway, C. Clifford; Chiao, J. W.; Wang, Chung-Xiou; Amin, Shantu; Whysner, John; Dai, Wei; Reinhardt, Joel; Chung, Fung-Lung

CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology, American Health Foundation, Valhalla, NY, 10595, USA

SOURCE: Cancer Research (2002), 62(1), 2-7

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To evaluate whether isothiocyanates (ITCs) compds. administered after carcinogen treatment inhibit lung tumorigenesis, the authors investigated in A/J mice the effects of the N-acetylcysteine (NAC) conjugates of benzyl (BITC-NAC) and phenethyl ITC (PEITC-NAC) in the diet (15 mol/g) administered after a single dose of 20 mol benzo(a)pyrene [B(a)P]. The formation of lung adenomas was examined 140 days after B(a)P dosing. Both the BITC-NAC and PEITC-NAC-treated groups showed a significant reduction in lung tumor multiplicity from 6.1 3.1 tumors/mouse in the B(a)P group fed the control diet to 3.7 2.9 and 3.4 2.7 tumors/mouse ($P = 0.018$ and 0.006 , resp.). To investigate the mechanisms of tumor inhibition, lung tissues were obtained at 21, 84, and 140 days at interim sacrifices during the bioassay. These tissues showed a significant increase in apoptosis as determined by in situ end-labeling for both ITC-NAC-treated groups. The mitogen-activated protein (MAP) kinase pathway was activated in the ITC-NAC-treated groups. The activation of c-Jun NH₂-terminal kinase was higher in the BITC-NAC and PEITC-NAC groups when compared with B(a)P-treated control. The phosphorylation of p38 and extracellular signal-regulated kinases (ErKs) 1 and 2 was also induced by these treatments. To determine the downstream target of MAP kinases, activator protein-1 (AP-1) and nuclear factor- κ B activities were evaluated by gel shift assay. The AP-1 binding activity was remarkably increased in lung tissue from both the BITC-NAC and PEITC-NAC groups. No change in nuclear factor-B binding activity was found, however. Phosphorylation of p53 was also higher than the constitutive levels in both ITC-NAC-treated groups, but no induction of p53 expression was detected. This study demonstrates the chemopreventive efficacy of the NAC conjugates of PEITC and BITC administered in the diet after a single dose of B(a)P for lung tumorigenesis and provides the first in vivo evidence that activation of MAP kinases, AP-1 transcription factors, p53 phosphorylation, and the induction of apoptosis may be involved in the chemopreventive activity of these compds.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2001:240696 CAPLUS
DOCUMENT NUMBER: 135:70820
TITLE: Modulation of biomarkers by chemopreventive agents in smoke-exposed rats
AUTHOR(S): Izzotti, Alberto; Balansky, Roumen M.; D'Agostini, Francesco; Bennicelli, Carlo; Myers, Steven R.; Grubbs, Clinton J.; Lubet, Ronald A.; Kelloff, Gary J.; De Flora, Silvio
CORPORATE SOURCE: Department of Health Sciences, University of Genoa, Genoa, I-16132, Italy
SOURCE: Cancer Research (2001), 61(6), 2472-2479
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chemoprevention opens new perspectives in the prevention of cancer and other chronic degenerative diseases associated with tobacco smoking, exploitable in current smokers and, even more, in ex-smokers and passive smokers. Evaluation of biomarkers in animal models is an essential step for the preclin. assessment of efficacy and safety of potential chemopreventive agents. Groups of Sprague Dawley rats were exposed whole body to a mixture of mainstream and sidestream cigarette smoke for 28 consecutive days. Five chemopreventive agents were given either with drinking water (N-acetyl-L-cysteine, 1 g/kg body weight/day) or with the diet (1,2-dithiole-3-thione, 400 mg; Oltipraz, 400 mg; phenethyl isothiocyanate, 500 mg; and 5,6-benzoflavone, 500 mg/kg diet). The monitored biomarkers included: DNA adducts in bronchoalveolar lavage cells, tracheal epithelium, lung and heart; oxidative damage to pulmonary DNA; Hb adducts of 4-aminobiphenyl and benzo(a)pyrene-7,8-diol-9,10-epoxide; micronucleated and polynucleated alveolar macrophages and micronucleated polychromatic erythrocytes in bone marrow. Exposure of rats to smoke resulted in dramatic alterations of all investigated parameters. N-Acetyl-L-cysteine, phenylethyl isothiocyanate, and 5,6-benzoflavone exerted a significant protective effect on all alterations. 1,2-Dithiole-3-thione was a less effective inhibitor and exhibited both a systemic toxicity and genotoxicity in alveolar macrophages, whereas its substituted analog Oltipraz showed limited protective effects in this model. Interestingly, combination of N-acetyl-L-cysteine with Oltipraz was the most potent treatment, resulting in an additive or more than additive inhibition of smoke-related DNA adducts in the lung and Hb adducts. These results provide evidence for the differential ability of test agents to modulate smoke-related biomarkers in the respiratory tract and other body compartments and highlight the potential advantages in combining chemopreventive agents working with distinctive mechanisms.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2001:553247 CAPLUS
DOCUMENT NUMBER: 135:266822
TITLE: Decomposition rates of isothiocyanate conjugates determine their activity as inhibitors of cytochrome p450 enzymes
AUTHOR(S): Conaway, C. Clifford; Krzeminski, Jacek; Amin, Shantu; Chung, Fung-Lung
CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology, American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Chemical Research in Toxicology (2001), 14(9), 1170-1176
CODEN: CRTOEC; ISSN: 0893-228X

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thiol conjugates of isothiocyanates (thiol-ITCs) are metabolites of ITCs formed in the mercapturic acid pathway in mammals. They are effective chemopreventive agents in mouse lung tumor bioassays and in other models. Thiol-ITCs are inhibitors of P450s, but it has not been determined if P 450 inhibition is due to conjugates themselves or to parent ITCs released by deconjugation reactions. In studies of mechanism of chemopreventive action of thiol-ITCs, rates of deconjugation of Cys, GSH, and N-acetyl-L-cysteine (NAC) conjugates of benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), 6-phenylhexyl isothiocyanate (PHITC), and sulforaphane (SFN), expressed as the first-order rate constant k_1 and the half-life of decomposition

$Dt_{1/2}$, were measured in aqueous solns. at pH 7.4 and 37°. The $Dt_{1/2}$ s for the Cys conjugates were severalfold shorter than the $Dt_{1/2}$ s for resp. GSH conjugates, while the $Dt_{1/2}$ s for the NAC conjugates were the longest. Cleavage of thiol conjugates was pH dependent, much slower under acidic conditions than at pH 7.4. Inhibition of P 450 enzymes by thiol-ITCs was followed using PROD (pentoxyresorufin O-dealkylation) for P 450 2B1 and EROD (ethoxyresorufin O-dealkylation) for P 450 1A1. The inhibition of PROD and EROD by aqueous thiol-ITCs increased with preincubation time and was roughly parallel to the extent of decomposition of the conjugate that had occurred, indicating that both potency of the resp. parent ITC and the rate of reductive cleavage of the conjugate influenced enzyme inhibition. In the presence of 250-1000 μ M GSH, comparable to physiol. levels, rates of deconjugation of thiol-ITCs were markedly reduced; inhibition of PROD was also proportionately reduced. Slow rates of decomposition of thiol-ITCs anticipated in plasma and tissues suggests that inhibition of P 450 enzymes involved in carcinogen activation by ITCs released from thiol-ITCs may not be a principal mechanism for their tumor inhibitory activity; other mechanisms probably contribute to their chemopreventive activity.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 22 OF 34 MEDLINE on STN

ACCESSION NUMBER: 2001254980 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11353135

TITLE: Cell-type specific differences in glutamate cysteine ligase transcriptional regulation demonstrate independent subunit control.

AUTHOR: Dahl E L; Mulcahy R T

CORPORATE SOURCE: Environmental Toxicology Center and Department of Pharmacology, University of Wisconsin, Madison, Wisconsin 53792, USA.

CONTRACT NUMBER: CA57549 (United States NCI NIH HHS)
ES09749 (United States NIEHS NIH HHS)
T32 ES0715 (United States NIEHS NIH HHS)

SOURCE: Toxicological sciences : an official journal of the Society of Toxicology, (2001 Jun) Vol. 61, No. 2, pp. 265-72.
Journal code: 9805461. ISSN: 1096-6080.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108

ENTRY DATE: Entered STN: 13 Aug 2001

Last Updated on STN: 13 Aug 2001

Entered Medline: 9 Aug 2001

AB Glutamate cysteine ligase (GCL; also referred to as gamma-glutamylcysteine synthetase, GCS) catalyzes the rate-limiting step of glutathione synthesis. The GCL holoenzyme is composed of a catalytic (GCLC; also called GCS(h)) and a modifier (GCLM; also called GCS(l)) subunit, each encoded by a unique gene. Wild-type and mutant promoter/luciferase reporter transgenes containing the promoter region of each GCL subunit gene were transfected into A549 (lung carcinoma), HEK 293 (transformed embryonic kidney), HepG2 (hepatocellular carcinoma), and RD (skeletal muscle rhabdomyosarcoma) cells to examine potential cell-type related differences in transcriptional regulation. In A549, HepG2, and RD cells, maximal basal expression of the GCLC transgene required the full-length (-3802 bp) promoter. Maximal expression in HEK 293 cells was uniquely directed by cis-elements contained within the -2752 to -1286 bp fragment of the promoter. No differences in GCLM promoter function were detected among these 4 cell lines. GCL subunit induction in each cell line by pyrrolidine dithiocarbamate (PDTC), phenethyl isothiocyanate (PEITC), and beta-naphthoflavone (beta-NF) was examined by RNase protection assays. Although both genes were similarly induced in HepG2 cells by beta-NF, PDTC, and PEITC, neither was induced by beta-NF in A549, HEK 293, and RD cells. PDTC and PEITC induced GCLM to a much greater extent than GCLC in HEK 293 cells and failed to induce GCLC in RD cells. Neither subunit was induced by any of the agents in A549 cells. These studies indicate that the GCL subunit genes are independently regulated and display cell-type specific differences in both basal and inducible expression.

L6 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 2001:65774 CAPLUS

DOCUMENT NUMBER: 135:102077

TITLE: Successful and not so successful chemoprevention of tobacco smoke-induced lung tumors

AUTHOR(S): Witschi, Hanspeter

CORPORATE SOURCE: ITEH and Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, USA

SOURCE: Experimental Lung Research (2000), 26(8), 743-755
CODEN: EXLRDA; ISSN: 0190-2148

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Strain A/J mice underwent whole body exposure for 6 h a day, 5 days a week, for 5 mo to a mixture of cigarette sidestream and mainstream smoke (89%-11%; total suspended particulates 80-150 mg/m³), then were kept for another 4 mo in air before being killed for scoring of lung tumors. In 7 independent expts., lung tumor multiplicity was significantly increased in all 7 trials and lung tumor incidence in 5. When animals were kept for 9 mo in smoke, lung tumor multiplicity was not significantly higher than in controls, although lung tumor incidence was. The following chemopreventive agents were evaluated: green tea, phenethyl isothiocyanate (PEITC), acetylsalicylic acid (ASA), N-acetylcysteine (NAC), p-XSC (1,4-phenylene-bis[methylene]selenocyanate), d-limonene (DL), and a mixture of PEITC and BITC (benzyl isothiocyanate). In animals exposed to tobacco smoke, none of these agents reduced lung tumor multiplicity or incidence. As a control, the effects of the same agents were examined in A/J mice initiated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or urethane. In mice injected with NNK, green tea and ASA did not reduce lung tumor multiplicities and NAC had no effect on urethane-induced lung tumors, whereas PEITC, p-XSC and DL reduced NNK-induced tumor multiplicities to 20% to 50% of control

values. On the other hand, dietary mixture of myo-inositol and dexamethasone was not only highly protective against NNK, but reduced lung tumor multiplicities and incidence in smoke-exposed animals to control values. This effect was also seen when the animals were fed the myo-inositol-dexamethasone mixture once they were removed from smoke. It is concluded that in animal studies it might be preferable to evaluate the effectiveness of putative chemopreventive agents against full tobacco smoke rather than against selected model compds. The observations made with myo-inositol-dexamethasone suggest that people who have recently quit smoking might benefit the most from active chemoprevention.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 14

ACCESSION NUMBER: 1998:701463 CAPLUS

DOCUMENT NUMBER: 130:60726

TITLE: The effects of phenethyl isothiocyanate, N-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain A/J mice

AUTHOR(S): Witschi, Hanspeter; Espiritu, Imelda; Yu, Mang; Willits, Neil H.

CORPORATE SOURCE: Institute of Toxicology and Environmental Health, University of California, Davis, CA, 95616-8615, USA

SOURCE: Carcinogenesis (1998), 19(10), 1789-1794

CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Male and female strain A/J mice were exposed to a mixture of cigarette side-stream and mainstream smoke at a chamber concentration of total suspended particulates of 82.5 mg/m³. Exposure time was 6 h/day, 5 days/wk for 5 mo. The animals were allowed to recover for another 4 mo in filtered air before sacrifice and lung tumor count. Male animals were fed either 0.2% N-acetylcysteine (NAC) or 0.05% phenethyl isothiocyanate (PEITC) in diet AIN-76A with 5% corn oil added. Female animals received normal laboratory chow and were given a 1.25% extract

of green tea in the drinking water. Corresponding control groups were fed diets without NAC or PEITC or given plain tap water. Exposure to tobacco smoke increased lung tumor multiplicity to 1.1-1.6 tumors/lung, significantly higher than control values (0.5-1.0 tumors/lung). None of the putative chemopreventive agents (NAC, PEITC or green tea extract) had a protective effect. In pos. control expts., PEITC significantly reduced both lung tumor multiplicity and incidence in mice treated with the tobacco smoke-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). In mice treated with three different doses of urethane and fed NAC in the diet, a significant reduction in lung tumor multiplicity was found only at one dose level. Green tea extract did not reduce lung tumor multiplicity in animals treated with a single dose of NNK. It was concluded that successful chemoprevention of tobacco smoke-induced lung tumorigenesis might require administration of several chemopreventive agents rather than just a single one.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 15

ACCESSION NUMBER: 1997:779689 CAPLUS

DOCUMENT NUMBER: 128:110369

ORIGINAL REFERENCE NO.: 128:21485a,21488a

TITLE: Chemopreventive activity of thiol conjugates of isothiocyanates for lung tumorigenesis
AUTHOR(S): Jiao, Ding; Smith, Theresa J.; Yang, Chung S.; Pittman, Brian; Desai, Dhimant; Amin, Shantu; Chung, Fung-Lung
CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology, American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Carcinogenesis (1997), 18(11), 2143-2147
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of L-cysteine (L-Cys), glutathione (GSH), and N-acetyl-L-cysteine (NAC) conjugates of phenethyl (PEITC), benzyl (BITC), and 6-phenylhexyl isothiocyanate (PHITC) were studied for their inhibitory activity toward metabolic activation of the tobacco-specific nitrosamine 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in mouse lung microsomes. Selected compds., PEITC, PEITC-GSH, PEITC-NAC and PHITC-NAC, were also assayed for the potential chemopreventive activity toward NNK-induced lung tumorigenesis in A/J mice. Results showed that PEITC and its conjugates inhibited NNK metabolism with decreasing potency: PEITC < PEITC-GSH > PEITC - Cys > PEITC-NAC. PHITC and its GSH and NAC conjugates exhibited nearly 10 times higher inhibitory activity toward NNK metabolism than PEITC counterparts. In the tumor bioassay, as expected, the conjugates exhibited inhibitory activity against lung tumorigenesis induced by NNK. PEITC-GSH was not inhibitory at 4 $\mu\text{mol}/\text{mouse}$, but it inhibited .apprx.32% of lung tumor multiplicity at 8 $\mu\text{mol}/\text{mouse}$. PEITC-NAC at 5 and 20 $\mu\text{mol}/\text{mouse}$ both inhibited .apprx.30% tumor multiplicity. Among all the conjugates examined, PHITC-NAC was the most potent. At a 5- μmol dose, it completely inhibited tumor multiplicity and incidence to the background level observed in the control group. These results revealed that the structure-activity relationships of the conjugates are similar to those found with their parent isothiocyanates (ITCs), i.e., the potency increased with the increasing alkyl chain length from two to six carbons in arylalkyl ITCs, suggesting that a common active species is involved. The inhibitory activity of ITC conjugates and the expected low toxicity make thiol conjugates of ITC a promising new series of chemopreventive agents.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 1996:747991 CAPLUS
DOCUMENT NUMBER: 126:98839
ORIGINAL REFERENCE NO.: 126:18913a,18916a
TITLE: Inhibition of rat liver cytochrome of P450 isoenzymes by isothiocyanates and their conjugates: a structure-activity relationship study
AUTHOR(S): Conaway, C. Clifford; Jiao, Ding; Chung, Fung-Lung
CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology, American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Carcinogenesis (1996), 17(11), 2423-2427
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of arylalkyl and alkyl isothiocyanates, and their glutathione, cysteine, and N-acetylcysteine conjugates were used to study their inhibitory activity toward the dealkylation of ethoxyresorufin (EROD), pentoxyresorufin (PROD), and methoxyresorufin (MROD) in liver

microsomes obtained from the 3-methylcholanthrene or phenobarbital-treated rats. These reactions are predominantly mediated by cytochrome P 450 (P 450) isoenzymes 1A1 and 1A2, 2B1 and 1A2, resp. All isothiocyanates inhibited PROD more readily than EROD. Increases in the alkyl chain length of arylalkyl isothiocyanates to C6 resulted in an increased inhibitory potency in these assays; at longer alkyl chain lengths (C8-C130) the inhibitory potency declined. The IC50s for phenethyl isothiocyanate (PEITC) were 47, 46 and 1.8 μ M for EROD, MROD and PROD, resp. Substitution of an addnl. Ph group on PEITC also increased the inhibitory potency; the IC50s for 1,2-diphenylethyl isothiocyanate (1,2-DPEITC) and 2,2-diphenylethyl isothiocyanate (2,2-DPEITC) were 0.9 and 0.26 μ M for EROD, and 0.045 and 0.13 μ M for PROD, resp. The relative inhibitory potency of PEITC and its conjugates was N-acetylcysteine-PEITC (PEITC-NAC) < glutathione-PEITC (PEITC-GSH) < cysteine-PEITC (PEITC-CYS) < PEITC. The observations that the parent isothiocyanates were more potent inhibitors than the conjugates suggest that dissociation of the conjugate is required for activity. Naturally occurring alkyl isothiocyanates, sulforaphane (SFO) and allyl isothiocyanate (AITC), were very weak inhibitors in the assays. These results suggest the potential of isothiocyanates as structural probes for studying P 450 isoenzymes. In addition, the inhibitory activity of isothiocyanates for PROD correlated with the previously demonstrated tumor inhibitory potency in (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) induced A/J mouse lung tumor bioassays, which supports earlier findings that P 450 2B1 is one of the major isoenzymes involved in NNK activation and that inhibition of this isoenzyme is an important mechanism for the chemopreventive activity of isothiocyanates.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 17

ACCESSION NUMBER: 1996:104627 CAPLUS

DOCUMENT NUMBER: 124:193641

ORIGINAL REFERENCE NO.: 124:35515a,35518a

TITLE: Chemopreventive efficacy of arylalkyl isothiocyanates and N-acetylcysteine for lung tumorigenesis in Fischer rats

AUTHOR(S): Chung, Fung-Lung; Kelloff, Gary; Steele, Vernon; Pittman, Brian; Zang, Edith; Jiao, Ding; Rigotty, Jeffrey; Choi, Chang-In; Rivenson, Abraham

CORPORATE SOURCE: Div. Carcinogenesis Mol. Epidemiol., American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595, USA

SOURCE: Cancer Research (1996), 56(4), 772-8

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study is to evaluate the efficacy of three promising sulfur-containing compds., 6-phenylhexyl isothiocyanate (PHITC), phenethyl isothiocyanate (PEITC), and N-acetylcysteine (NAC), as chemopreventive agents in a long-term bioassay for lung tumorigenesis in F34 rats. PEITC occurs as a constituent of certain cruciferous vegetables, PHITC is a synthetic homolog, and NAC is an endogenous substance. Male F344 rats were treated with the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) by s.c. injection at a dose of 1.5 mg/kg body weight three times weekly for 20 wk. This dose regimen induced a 67% tumor incidence in the lung, a major target organ of NNK. PHITC or PEITC administered in the diet for 22 wk, a period covering from 1 wk before to 1 wk after the NNK treatment, exhibited significant inhibition

of lung tumorigenesis induced by NNK. The lung tumor incidences in the NNK-treated groups, fed a diet containing 4 mmol/kg (876 ppm) or 2 mmol/kg (438 ppm) PHITC, were 24 and 19% and were 9 and 17% in groups fed PEITC at concns. of 8 mmol/kg (1304 ppm) or 4 mmol/kg (652 ppm), resp. In contrast to isothiocyanates, NAC given in the diet at 80 mmol/kg (13056 ppm) or 40 mmol/kg (6528 ppm) exerted no inhibitory effects on the NNK-induced lung tumorigenesis. At the dose studied, NNK did not induce liver and pancreatic tumors in the treated animals, but a significant increase of nasal cavity tumor incidence was observed in the NNK-treated group. However, none of the test compds. showed any effect on the tumorigenesis in this tissue. This study demonstrated that PHITC and PEITC were potent chemopreventive agents for the NNK-induced lung tumorigenesis in F344 rats, whereas NAC was not active at all. These results support further evaluation of these compds. in chemoprevention studies.

L6 ANSWER 28 OF 34 MEDLINE on STN
 ACCESSION NUMBER: 1997141809 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 8988067
 TITLE: Decrease of plasma and urinary oxidative metabolites of acetaminophen after consumption of watercress by human volunteers.
 AUTHOR: Chen L; Mohr S N; Yang C S
 CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy, Rutgers University, Piscataway, NJ 08855, USA.
 CONTRACT NUMBER: ES03938 (United States NIEHS NIH HHS)
 ES05022 (United States NIEHS NIH HHS)
 ES05693 (United States NIEHS NIH HHS)
 SOURCE: Clinical pharmacology and therapeutics, (1996 Dec) Vol. 60, No. 6, pp. 651-60.
 Journal code: 0372741. ISSN: 0009-9236.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (CLINICAL TRIAL)
 (CONTROLLED CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 199701
 ENTRY DATE: Entered STN: 19 Feb 1997
 Last Updated on STN: 29 Jan 1999
 Entered Medline: 23 Jan 1997
 AB To investigate the effect of the consumption of watercress (*Nasturtium officinale* R. Br.), a cruciferous vegetable, on acetaminophen metabolism, the pharmacokinetics of acetaminophen and its metabolites were studied in a crossover trial of human volunteers. A single oral dose of acetaminophen (1 gm) was given 10 hours after ingestion of watercress homogenates (50 gm). In comparison with acetaminophen only, the ingestion of watercress resulted in a significant reduction in the area under the plasma cysteine acetaminophen (Cys-acetaminophen) concentration-time curve and in the peak plasma Cys-acetaminophen concentration by 28% +/- 3% and by 21% +/- 4% (mean +/- SE; n = 7; p < 0.005), respectively. Correspondingly, the Cys-acetaminophen formation rate constant and Cys-acetaminophen formation fraction were decreased by 55% +/- 9% and 52% +/- 7% (p < 0.01), respectively. Consistent with the results obtained from the plasma, the total urinary excretion of Cys-acetaminophen in 24 hours was also reduced. A decrease of mercapturate acetaminophen, a Cys-acetaminophen metabolite, was also shown in the plasma and urine samples. However, the plasma pharmacokinetic processes and the urinary excretions of acetaminophen, acetaminophen glucuronide, and acetaminophen sulfate were not altered significantly by the watercress treatment. These results suggest that the consumption of

watercress causes a decrease in the levels of oxidative metabolites of acetaminophen, probably due to inhibition of oxidative metabolism of this drug.

L6 ANSWER 29 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1995:491327 CAPLUS
DOCUMENT NUMBER: 122:281655
ORIGINAL REFERENCE NO.: 122:51075a,51078a
TITLE: Preclinical efficacy evaluation of potential chemopreventive agents in animal carcinogenesis models: methods and results from the NCI Chemoprevention Drug Development Program
AUTHOR(S): Steele, Vernon E.; Moon, Richard C.; Lubet, Ronald A.; Grubbs, Clinton J.; Reddy, Bandaru S.; Wargovich, Michael; McCormick, David L.; Pereira, Michael A.; Crowell, James A.; et al.
CORPORATE SOURCE: DCPC, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Cellular Biochemistry (1994), (Suppl. 20), 32-54
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the NCI, Chemoprevention Branch drug development program, potential chemopreventive agents are evaluated for efficacy against chemical carcinogen-induced tumors in animal models. This paper summarizes the results of 144 agents in 352 tests using various animal efficacy models. Of these results, 146 were pos., representing 85 different agents. The target organs selected for the animals model are representative of high-incidence human cancers. The assays include inhibition of tumors induced by MNU in hamster trachea, DEN in hamster lung, AOM in rat colon (including inhibition of AOM-induced aberrant crypts), MAM in mouse colon, DMBA and MNU in rat mammary glands, DMBA promoted by TPA in mouse skin, and OH-BBN in mouse bladder. The agents tested may be classified into various pharmacol. and chemical structural categories that are relevant to their chemopreventive potential. These categories include antiestrogens, antiinflammatories (e.g., NSAIDs), antioxidants, arachidonic acid metabolism inhibitors, GST and GSH enhancers, ODC inhibitors, protein kinase C inhibitors, retinoids and carotenoids, organosulfur compds., calcium compds., vitamin D3 and analogs, and phenolic compds. (e.g., flavonoids). The various categories of compds. have different spectra of efficacy in animal models. In hamster lung, GSH-enhancing agents and antioxidants appear to have high potential for inhibiting carcinogenesis. In the colon, NSAIDs and other antiinflammatory agents appear particularly promising. Likewise, NSAIDs are very active in mouse bladder. In rat mammary glands, retinoids and antiestrogens (as would be expected) are efficacious. Several of the chems. evaluated also appear to be promising chemopreventive agents based on their activity in several of the animal models. Particularly, the ODC inhibitor DFMO was active in the colon, mammary glands, the bladder models, while the dithiolthione, oltipraz, was efficacious in all the models listed above (i.e., lung, colon, mammary glands, skin, and bladder).

L6 ANSWER 30 OF 34 MEDLINE on STN

ACCESSION NUMBER: 1993290258 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8512247
TITLE: Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis by compounds derived from cruciferous vegetables and green tea.
AUTHOR: Chung F L; Morse M A; Eklind K I; Xu Y

CORPORATE SOURCE: Division of Chemical Carcinogenesis American Health
Foundation, Valhalla, New York 10595.
CONTRACT NUMBER: CA-46535 (United States NCI NIH HHS)
CA-51830 (United States NCI NIH HHS)
SOURCE: Annals of the New York Academy of Sciences, (1993 May 28)
Vol. 686, pp. 186-201; discussion 201-2. Ref: 39
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 23 Jul 1993
Last Updated on STN: 23 Jul 1993
Entered Medline: 15 Jul 1993

AB We have shown that PEITC and I3C, both of cruciferous origin, inhibited lung tumor formation induced by the tobacco-specific nitrosamine NNK. The inhibition by PEITC is due largely to its inhibitory effect on the enzymes of NNK metabolism, whereas; the inhibition by I3C may be attributed to its ability to induce hepatic enzyme activity of NNK metabolism, which resulted in decreased availability of NNK to the lung. On a molar basis, PEITC is considerably more effective than I3C. PEITC was released upon consumption of watercress. The N-acetylcysteine conjugate of PEITC is a promising urinary marker for quantitating uptake of this dietary anticarcinogen in humans. These studies also showed that green tea polyphenol EGCG inhibited the NNK-induced lung tumorigenesis, probably due to its antioxidant property. These studies provide for the first time evidence for the involvement of free radicals in nitrosamine tumorigenesis. The mechanism by which free radicals are generated by NNK treatment is not yet known. The reduced levels of oxidative lesions in lung as a result of EGCG treatment may be related to its ability to reduce reactive oxygen species and/or to chelate iron ion resulting in a decreased production of hydroxyl radicals. Overall, these studies have identified ingredients in cruciferous vegetables and green tea that are inhibitory against lung tumorigenesis induced by NNK in rodents.

L6 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1992:439817 CAPLUS
DOCUMENT NUMBER: 117:39817
ORIGINAL REFERENCE NO.: 117:6838h,6839a
TITLE: New potential chemopreventive agents for lung
carcinogenesis of tobacco-specific nitrosamine
AUTHOR(S): Chung, Fung Lung; Morse, Mark A.; Eklind, Karin I.
CORPORATE SOURCE: American Health Found., Valhalla, NY, 10595, USA
SOURCE: Cancer Research (1992), 52(9, Suppl.), 2719s-2722s
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cigarette smoking is the major cause of lung cancer in humans. The continuous increase in the prevalence of cigarette smoking worldwide demands a practical means to circumvent this serious health problem. The authors research has focused on the development of new chemopreventive agents against lung carcinogenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Several aromatic isothiocyanates have been identified as effective inhibitors of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Phenethyl isothiocyanate, a natural constituent of cruciferous vegetables, protects F344 rats and A/J mice from 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung

tumorigenesis. The alkyl chain length in the aromatic isothiocyanates is an important structural feature for the inhibitory potency. The inhibitory efficacy increases as the alkyl chain elongates up to 6 carbon atoms. Thus, 6-phenylhexyl isothiocyanate is approx. 50 to 100 times more potent than phenethyl isothiocyanate. The remarkable efficiency of 6-phenylhexyl isothiocyanate suggests its potential as a chemopreventive agent in intervention trials. The tissue distribution and excretion of phenethyl isothiocyanate were studied in mice. Two major urinary metabolites were identified as the mercaptopyruvic acid and the N-acetylcysteine conjugates. A urinary marker was developed to quantitate the uptake of phenethyl isothiocyanate in humans after consumption of watercress, a cruciferous vegetable rich in gluconasturtiin, the glucosinolate precursor of phenethyl isothiocyanate. Considering the anticarcinogenic activity of phenethyl isothiocyanate, this marker may eventually be useful in assessing the role of dietary phenethyl isothiocyanate uptake in lung cancer risk.

L6 ANSWER 32 OF 34 MEDLINE on STN
 ACCESSION NUMBER: 1992224178 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 1563003
 TITLE: New potential chemopreventive agents for lung carcinogenesis of tobacco-specific nitrosamine.
 AUTHOR: Chung F L; Morse M A; Eklind K I
 CORPORATE SOURCE: American Health Foundation, Valhalla, New York 10595.
 CONTRACT NUMBER: CA-32272 (United States NCI NIH HHS)
 CA-41544 (United States NCI NIH HHS)
 CA-46535 (United States NCI NIH HHS)
 SOURCE: Cancer research, (1992 May 1) Vol. 52, No. 9 Suppl, pp. 2719s-2722s.
 Journal code: 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199205
 ENTRY DATE: Entered STN: 7 Jun 1992
 Last Updated on STN: 7 Jun 1992
 Entered Medline: 21 May 1992

AB Cigarette smoking is the major cause of lung cancer in humans. The continuous increase in the prevalence of cigarette smoking worldwide demands a practical means to circumvent this serious health problem. Our research has focused on the development of new chemopreventive agents against lung carcinogenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Several aromatic isothiocyanates have been identified as effective inhibitors of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Phenethyl isothiocyanate, a natural constituent of cruciferous vegetables, protects F344 rats and A/J mice from 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. The alkyl chain length in the aromatic isothiocyanates is an important structural feature for the inhibitory potency. The inhibitory efficacy increases as the alkyl chain elongates up to 6 carbon atoms. Thus, 6-phenylhexyl isothiocyanate is approximately 50 to 100 times more potent than phenethyl isothiocyanate. The remarkable efficiency of 6-phenylhexyl isothiocyanate suggests its potential as a chemopreventive agent in intervention trials. The tissue distribution and excretion of phenethyl isothiocyanate were studied in mice. Two major urinary metabolites were identified as the mercaptopyruvic acid and the N-acetylcysteine conjugates. A urinary marker was developed to

quantitate the uptake of phenethyl isothiocyanate in humans after consumption of watercress, a cruciferous vegetable rich in gluconasturtiin, the glucosinolate precursor of phenethyl isothiocyanate. Considering the anticarcinogenic activity of phenethyl isothiocyanate, this marker may eventually be useful in assessing the role of dietary phenethyl isothiocyanate uptake in lung cancer risk.

L6 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 18

ACCESSION NUMBER: 1994:293485 CAPLUS
DOCUMENT NUMBER: 120:293485
ORIGINAL REFERENCE NO.: 120:51579a,51582a
TITLE: Quantitation of human uptake of the anticarcinogen phenethyl isothiocyanate after a watercress meal
AUTHOR(S): Chung, F. L.; Morse, M. A.; Eklind, K. I.; Lewis, J.
CORPORATE SOURCE: Div. Chem. Carcinog., Am. Health Found., Valhalla, NY, 10595, USA
SOURCE: Cancer Epidemiology, Biomarkers & Prevention (1992), 1(5), 383-8
CODEN: CEBPE4; ISSN: 1055-9965
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phenethyl isothiocyanate (PEITC), a cruciferous vegetable constituent, inhibits the lung tumorigenesis induced by a potent tobacco-specific carcinogenic nitrosamine in animals. These results implicate dietary PEITC as a risk-reducing factor of lung cancers induced by smoking. To define the effect of dietary PEITC on human cancers, a method of measuring its uptake is needed. Since watercress is rich in gluconasturtiin, a glucosinolate precursor of PEITC, it was chosen to be the source of PEITC. Four individuals were asked to eat watercress as part of a breakfast meal, and 24-h urine samples were collected. A urinary metabolite was found, and its identity was confirmed as the N-acetylcysteine conjugate of PEITC by comparison with the synthetic standard using NMR and mass spectrometry. A dose-dependent excretion of this conjugate was observed. These results clearly showed that PEITC was released in the human body upon ingestion of watercress and suggest that the N-acetylcysteine conjugate of PEITC may be a useful marker for quantitating human exposure to this anticarcinogen as a tool for epidemiol. investigations.

L6 ANSWER 34 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1991:76760 CAPLUS
DOCUMENT NUMBER: 114:76760
ORIGINAL REFERENCE NO.: 114:12983a,12986a
TITLE: Distribution and metabolism of the natural anticarcinogen phenethyl isothiocyanate in A/J mice
AUTHOR(S): Eklind, Karin I.; Morse, Mark A.; Chung, Fung Lung
CORPORATE SOURCE: Div. Chem. Carcinog., American Health Found., Valhalla, NY, 10595, USA
SOURCE: Carcinogenesis (1990), 11(11), 2033-6
CODEN: CRNGDP; ISSN: 0143-3334
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The distribution and metabolism of phenethyl isothiocyanate (PEITC), a naturally occurring anticarcinogen, was investigated in A/J mice. Mice were administered 5 μ mol of [14 C]PEITC (2 μ Ci/mouse) by gavage and killed at 1, 2, 4, 8, 24, 48, or 72 h after dosing. Radioactivity present in the spleen, heart, liver, lung, kidney, brain, urine, and feces was measured. Lung, the target tissue of PEITC inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) lung

tumorigenesis, showed maximum radioactivity between 4 and 8 h after dosing, suggesting this time period would be optimal for maximal inhibition by PEITC in A/J mice. Approx. 50% of the total radioactivity was excreted within 24 h after dosing with nearly 80% of radioactivity found in urine and feces at 72 h. Two metabolites were isolated by reversed-phase HPLC from urine of mice treated with PEITC. The identities of these metabolites were determined by comparison with synthetic stds. and by NMR and MS. The major metabolite was a cyclic mercaptopyruvic acid conjugate, whereas the minor metabolite was an N-acetylcysteine conjugate. Approx. 25% of the administered dose of PEITC was excreted as the cyclic mercaptopyruvic acid conjugate and 10% as the N-acetylcysteine conjugate. These results suggest that urinary metabolites of PEITC may provide potentially useful dosimeters for this natural anticarcinogen.

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=> s isothiocyanate and (acetylcysteine or nac) and lung and (tumor? or neoplas? or
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L1 44 ISOTHIOCYANATE AND (ACETYLCYSTEINE OR NAC) AND LUNG AND (TUMOR?
OR NEOPLAS? OR CANCER?)

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L2 27 L1 NOT PY>2002

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L3 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2002:666445 CAPLUS

DOCUMENT NUMBER: 138:265227

TITLE: Inhibition of lung tumorigenesis
in A/J mice by

N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-cysteine and
myo-inositol, individually and in combination
AUTHOR(S): Hecht, Stephen S.; Upadhyaya, Pramod; Wang, Mingyao;
Bliss, Robin L.; McIntee, Edward J.; Kenney, Patrick
M. J.

CORPORATE SOURCE: University of Minnesota Cancer Center, Minneapolis,
MN, 55455, USA

SOURCE: Carcinogenesis (2002), 23(9), 1455-1461
CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Isothiocyanates, their N-acetylcysteine conjugates,
and myo-inositol (MI) are inhibitors of lung
tumorigenesis in A/J mice. However, chemoprevention by
combinations of these compds. in different temporal sequences has not been
examined This is important for developing practical approaches to
lung cancer chemoprevention in smokers and ex-smokers.
We used a tumor model in which A/J mice are treated with 8
weekly doses of benzo[a]pyrene (B[a]P) plus
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and killed 19 wk
after the final treatment. In Experiment 1, isothiocyanates or their
N-acetylcysteine conjugates were added to the diet (1 or 3
 $\mu\text{mol/g}$) from 1 wk before until 1 wk after carcinogen treatment. The
compds. were 2-phenethyl isothiocyanate (PEITC), 3-phenylpropyl
isothiocyanate (PPITC), N-acetyl-S-(N-benzylthiocarbamoyl)-L-
cysteine (BITC-NAC), N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-
cysteine (PEITC-NAC), and
N-acetyl-S-(N-3-phenylpropylthiocarbamoyl)-L-cysteine (PPITC-NAC
) . Significant redns. in lung tumor multiplicity were
observed in mice treated with PEITC, PEITC-NAC, PPITC and PPITC-
NAC. PEITC-NAC was chosen for combination studies with
MI (Experiment 2). Mice were treated with B[a]P plus NNK without or with
PEITC-NAC (3 $\mu\text{mol/g}$ diet), MI (55.5 $\mu\text{mol/g}$ diet), or
PEITC-NAC plus MI (3 μmol plus 55.5 $\mu\text{mol/g}$ diet).
Different temporal sequences of dietary addns. were investigated:
carcinogen treatment phase; post-carcinogen treatment phase; entire experiment;
50% of carcinogen treatment phase until termination; and 75% of carcinogen
treatment phase until termination. All treatments reduced lung
tumor multiplicity except PEITC-NAC post-carcinogen or
from 75% of the carcinogen treatment phase. Reduction of lung
tumor multiplicity by PEITC-NAC plus MI was greater than
that in the mice treated with the agents alone in all temporal sequences.
When all results were combined, PEITC-NAC plus MI was
significantly more effective than the agents alone. There was a

significant trend for reduction in lung tumor multiplicity with increased duration of treatment by the chemopreventive agents. These results provide a basis for further development of mixts. of PEITC-NAC and MI for chemoprevention of lung cancer.

OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2002:205671 CAPLUS

DOCUMENT NUMBER: 137:57131

TITLE: Expression of cyclin D1/2 in the lungs of strain A/J mice fed chemopreventive agents

AUTHOR(S): Witschi, Hanspeter; Espiritu, Imelda; Suffia, Marie; Pinkerton, Kent E.

CORPORATE SOURCE: Center for Health and the Environment and Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, 95616, USA

SOURCE: Carcinogenesis (2002), 23(2), 289-294

CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Male strain A mice were fed a diet containing chemopreventive agents. After 1 and 3 wk on the diets, lung nuclear fractions were examined for expression of cyclin D1/2 with western blot anal. In animals fed a diet containing a mixture of myoinositol and dexamethasone, a treatment found previously to be effective in preventing the development of tobacco smoke-induced lung tumors in A/J mice, cyclin D1/2 expression was reduced to 30-40% of control levels. A similar decrease in cyclin D1/2 expression was found when animals were fed either myoinositol or dexamethasone alone. Paradoxically, tobacco smoke by itself had a similar effect on cyclin D1/2 expression. On the other hand, several agents that had been previously found not to be effective against tobacco smoke carcinogenesis [phenethyl isothiocyanate, 1,4-phenylenebis(methylene)selenoisocyanate, N-acetylcysteine, acetylsalicylic acid, D-limonene and beta carotene] did not decrease cyclin D1/2 expression after 1 or 3 wk of feeding. It was concluded that expression of cyclin D1/2 might be a potentially useful marker in the identification of chemopreventive agents for tobacco smoke and could be of some help in the evaluation of their effects.

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

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L3 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2002:70893 CAPLUS

DOCUMENT NUMBER: 136:262469

TITLE: Inhibition of benzo(a)pyrene-induced lung tumorigenesis in A/J mice by dietary N-acetylcysteine conjugates of benzyl and phenethyl isothiocyanates during the postinitiation phase is associated with activation of mitogen-activated protein kinases and p53 activity and induction of apoptosis

AUTHOR(S): Yang, Yang-Ming; Conaway, C. Clifford; Chiao, J. W.; Wang, Chung-Xiou; Amin, Shantu; Whysner, John; Dai, Wei; Reinhardt, Joel; Chung, Fung-Lung

CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology,

SOURCE: American Health Foundation, Valhalla, NY, 10595, USA
Cancer Research (2002), 62(1), 2-7
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate whether isothiocyanates (ITCs) compds. administered after carcinogen treatment inhibit lung tumorigenesis, the authors investigated in A/J mice the effects of the N-acetylcysteine (NAC) conjugates of benzyl (BITC-NAC) and phenethyl ITC (PEITC-NAC) in the diet (15 mol/g) administered after a single dose of 20 mol benzo(a)pyrene [B(a)P]. The formation of lung adenomas was examined 140 days after B(a)P dosing. Both the BITC-NAC and PEITC-NAC-treated groups showed a significant reduction in lung tumor multiplicity from 6.1 3.1 tumors/mouse in the B(a)P group fed the control diet to 3.7 2.9 and 3.4 2.7 tumors/mouse (P = 0.018 and 0.006, resp.). To investigate the mechanisms of tumor inhibition, lung tissues were obtained at 21, 84, and 140 days at interim sacrifices during the bioassay. These tissues showed a significant increase in apoptosis as determined by in situ end-labeling for both ITC-NAC-treated groups. The mitogen-activated protein (MAP) kinase pathway was activated in the ITC-NAC-treated groups. The activation of c-Jun NH2-terminal kinase was higher in the BITC-NAC and PEITC-NAC groups when compared with B(a)P-treated control. The phosphorylation of p38 and extracellular signal-regulated kinases (ErKs) 1 and 2 was also induced by these treatments. To determine the downstream target of MAP kinases, activator protein-1 (AP-1) and nuclear factor- κ B activities were evaluated by gel shift assay. The AP-1 binding activity was remarkably increased in lung tissue from both the BITC-NAC and PEITC-NAC groups. No change in nuclear factor-B binding activity was found, however. Phosphorylation of p53 was also higher than the constitutive levels in both ITC-NAC-treated groups, but no induction of p53 expression was detected. This study demonstrates the chemopreventive efficacy of the NAC conjugates of PEITC and BITC administered in the diet after a single dose of B(a)P for lung tumorigenesis and provides the first in vivo evidence that activation of MAP kinases, AP-1 transcription factors, p53 phosphorylation, and the induction of apoptosis may be involved in the chemopreventive activity of these compds.

OS.CITING REF COUNT: 80 THERE ARE 80 CAPLUS RECORDS THAT CITE THIS RECORD (80 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001199428 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11289117
TITLE: Modulation of biomarkers by chemopreventive agents in smoke-exposed rats.
AUTHOR: Izzotti A; Balansky R M; Dagostini F; Bennicelli C; Myers S R; Grubbs C J; Lubet R A; Kelloff G J; De Flora S
CORPORATE SOURCE: Department of Health Sciences, University of Genoa, Italy.
CONTRACT NUMBER: N01-CN-75008 (United States NCI NIH HHS)
SOURCE: Cancer research, (2001 Mar 15) Vol. 61, No. 6, pp. 2472-9. Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 2 May 2001
Last Updated on STN: 2 May 2001
Entered Medline: 26 Apr 2001

AB Chemoprevention opens new perspectives in the prevention of cancer and other chronic degenerative diseases associated with tobacco smoking, exploitable in current smokers and, even more, in exsmokers and passive smokers. Evaluation of biomarkers in animal models is an essential step for the preclinical assessment of efficacy and safety of potential chemopreventive agents. Groups of Sprague Dawley rats were exposed whole body to a mixture of mainstream and sidestream cigarette smoke for 28 consecutive days. Five chemopreventive agents were given either with drinking water (N-acetyl-L-cysteine, 1 g/kg body weight/day) or with the diet (1,2-dithiole-3-thione, 400 mg; Oltipraz, 400 mg; phenethyl isothiocyanate, 500 mg; and 5,6-benzoflavone, 500 mg/kg diet). The monitored biomarkers included: DNA adducts in bronchoalveolar lavage cells, tracheal epithelium, lung and heart; oxidative damage to pulmonary DNA; hemoglobin adducts of 4-aminobiphenyl and benzo(a)pyrene-7,8-diol-9,10-epoxide; micronucleated and polynucleated alveolar macrophages and micronucleated polychromatic erythrocytes in bone marrow. Exposure of rats to smoke resulted in dramatic alterations of all investigated parameters. N-Acetyl-L-cysteine, phenylethyl isothiocyanate, and 5,6-benzoflavone exerted a significant protective effect on all alterations. 1,2-Dithiole-3-thione was a less effective inhibitor and exhibited both a systemic toxicity and genotoxicity in alveolar macrophages, whereas its substituted analogue Oltipraz showed limited protective effects in this model. Interestingly, combination of N-acetyl-L-cysteine with Oltipraz was the most potent treatment, resulting in an additive or more than additive inhibition of smoke-related DNA adducts in the lung and hemoglobin adducts. These results provide evidence for the differential ability of test agents to modulate smoke-related biomarkers in the respiratory tract and other body compartments and highlight the potential advantages in combining chemopreventive agents working with distinctive mechanisms.

L3 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2001:553247 CAPLUS

DOCUMENT NUMBER: 135:266822

TITLE: Decomposition rates of isothiocyanate
conjugates determine their activity as inhibitors of
cytochrome p450 enzymes

AUTHOR(S): Conaway, C. Clifford; Krzeminski, Jacek; Amin, Shantu;
Chung, Fung-Lung

CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology,
American Health Foundation, Valhalla, NY, 10595, USA

SOURCE: Chemical Research in Toxicology (2001), 14(9),
1170-1176

CODEN: CRTOEC; ISSN: 0893-228X

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thiol conjugates of isothiocyanates (thiol-ITCs) are metabolites of ITCs formed in the mercapturic acid pathway in mammals. They are effective chemopreventive agents in mouse lung tumor bioassays and in other models. Thiol-ITCs are inhibitors of P450s, but it has not been determined if P 450 inhibition is due to conjugates themselves or to parent ITCs released by deconjugation reactions. In studies of mechanism of chemopreventive action of thiol-ITCs, rates of deconjugation of Cys, GSH, and N-acetyl-L-cysteine (NAC) conjugates of benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), 6-phenylhexyl isothiocyanate (PHITC), and sulforaphane (SFN), expressed as the first-order rate constant k_1 and the half-life of decomposition

Dt1/2, were measured in aqueous solns. at pH 7.4 and 37°. The Dt1/2s for the Cys conjugates were severalfold shorter than the Dt1/2s for resp. GSH conjugates, while the Dt1/2s for the NAC conjugates were the longest. Cleavage of thiol conjugates was pH dependent, much slower under acidic conditions than at pH 7.4. Inhibition of P 450 enzymes by thiol-ITCs was followed using PROD (pentoxiresorufin O-dealkylation) for P 450 2B1 and EROD (ethoxyresorufin O-dealkylation) for P 450 1A1. The inhibition of PROD and EROD by aqueous thiol-ITCs increased with preincubation time and was roughly parallel to the extent of decomposition of the conjugate that had occurred, indicating that both potency of the resp. parent ITC and the rate of reductive cleavage of the conjugate influenced enzyme inhibition. In the presence of 250-1000 µM GSH, comparable to physiol. levels, rates of deconjugation of thiol-ITCs were markedly reduced; inhibition of PROD was also proportionately reduced. Slow rates of decomposition of thiol-ITCs anticipated in plasma and tissues suggests that inhibition of P 450 enzymes involved in carcinogen activation by ITCs released from thiol-ITCs may not be a principal mechanism for their tumor inhibitory activity; other mechanisms probably contribute to their chemopreventive activity.

OS.CITING REF COUNT: 54 THERE ARE 54 CAPLUS RECORDS THAT CITE THIS RECORD (55 CITINGS)
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L3 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2001:65774 CAPLUS

DOCUMENT NUMBER: 135:102077

TITLE: Successful and not so successful chemoprevention of tobacco smoke-induced lung tumors

AUTHOR(S): Witschi, Hanspeter

CORPORATE SOURCE: ITEH and Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, USA

SOURCE: Experimental Lung Research (2000), 26(8), 743-755
 CODEN: EXLRDA; ISSN: 0190-2148

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Strain A/J mice underwent whole body exposure for 6 h a day, 5 days a week, for 5 mo to a mixture of cigarette sidestream and mainstream smoke (89%-11%; total suspended particulates 80-150 mg/m³), then were kept for another 4 mo in air before being killed for scoring of lung tumors. In 7 independent expts., lung tumor multiplicity was significantly increased in all 7 trials and lung tumor incidence in 5. When animals were kept for 9 mo in smoke, lung tumor multiplicity was not significantly higher than in controls, although lung tumor incidence was. The following chemopreventive agents were evaluated: green tea, phenethyl isothiocyanate (PEITC), acetylsalicylic acid (ASA), N-acetylcysteine (NAC), p-XSC (1,4-phenylene-bis[methylene]selenocyanate), d-limonene (DL), and a mixture of PEITC and BITC (benzyl isothiocyanate). In animals exposed to tobacco smoke, none of these agents reduced lung tumor multiplicity or incidence. As a control, the effects of the same agents were examined in A/J mice initiated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or urethane. In mice injected with NNK, green tea and ASA did not reduce lung tumor multiplicities and NAC had no effect on urethane-induced lung tumors, whereas PEITC, p-XSC and DL reduced NNK-induced tumor multiplicities to 20% to 50% of control values. On the other hand, dietary mixture of myo-inositol and dexamethasone was not only highly protective against NNK, but reduced

lung tumor multiplicities and incidence in smoke-exposed animals to control values. This effect was also seen when the animals were fed the myo-inositol-dexamethasone mixture once they were removed from smoke. It is concluded that in animal studies it might be preferable to evaluate the effectiveness of putative chemopreventive agents against full tobacco smoke rather than against selected model compds. The observations made with myo-inositol-dexamethasone suggest that people who have recently quit smoking might benefit the most from active chemoprevention.

OS.CITING REF COUNT: 39 THERE ARE 39 CAPLUS RECORDS THAT CITE THIS RECORD (39 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 1998:701463 CAPLUS

DOCUMENT NUMBER: 130:60726

TITLE: The effects of phenethyl isothiocyanate, N-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain A/J mice

AUTHOR(S): Witschi, Hanspeter; Espiritu, Imelda; Yu, Mang; Willits, Neil H.

CORPORATE SOURCE: Institute of Toxicology and Environmental Health, University of California, Davis, CA, 95616-8615, USA

SOURCE: Carcinogenesis (1998), 19(10), 1789-1794

CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Male and female strain A/J mice were exposed to a mixture of cigarette side-stream and mainstream smoke at a chamber concentration of total suspended particulates of 82.5 mg/m³. Exposure time was 6 h/day, 5 days/wk for 5 mo. The animals were allowed to recover for another 4 mo in filtered air before sacrifice and lung tumor count. Male animals were fed either 0.2% N-acetylcysteine (NAC) or 0.05% phenethyl isothiocyanate (PEITC) in diet AIN-76A with 5% corn oil added. Female animals received normal laboratory chow and were given a 1.25% extract of green tea in the drinking water. Corresponding control groups were fed diets without NAC or PEITC or given plain tap water. Exposure to tobacco smoke increased lung tumor multiplicity to 1.1-1.6 tumors/lung, significantly higher than control values (0.5-1.0 tumors/lung). None of the putative chemopreventive agents (NAC, PEITC or green tea extract) had a protective effect. In pos. control expts., PEITC significantly reduced both lung tumor multiplicity and incidence in mice treated with the tobacco smoke-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). In mice treated with three different doses of urethane and fed NAC in the diet, a significant reduction in lung tumor multiplicity was found only at one dose level. Green tea extract did not reduce lung tumor multiplicity in animals treated with a single dose of NNK. It was concluded that successful chemoprevention of tobacco smoke-induced lung tumorigenesis might require administration of several chemopreventive agents rather than just a single one.

OS.CITING REF COUNT: 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (52 CITINGS)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 1997:779689 CAPLUS

DOCUMENT NUMBER: 128:110369

ORIGINAL REFERENCE NO.: 128:21485a,21488a
TITLE: Chemopreventive activity of thiol conjugates of
isothiocyanates for lung
tumorigenesis
AUTHOR(S): Jiao, Ding; Smith, Theresa J.; Yang, Chung S.;
Pittman, Brian; Desai, Dhimant; Amin, Shantu; Chung,
Fung-Lung
CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology,
American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Carcinogenesis (1997), 18(11), 2143-2147
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of L-cysteine (L-Cys), glutathione (GSH), and N-acetyl-L-cysteine
(NAC) conjugates of phenethyl (PEITC), benzyl (BITC), and
6-phenylhexyl isothiocyanate (PHITC) were studied for their
inhibitory activity toward metabolic activation of the tobacco-specific
nitrosamine 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in mouse
lung microsomes. Selected compds., PEITC, PEITC-GSH, PEITC-
NAC and PHITC-NAC, were also assayed for the potential
chemopreventive activity toward NNK-induced lung
tumorigenesis in A/J mice. Results showed that PEITC and its
conjugates inhibited NNK metabolism with decreasing potency: PEITC < PEITC-GSH
> PEITC - Cys > PEITC-NAC. PHITC and its GSH and NAC
conjugates exhibited nearly 10 times higher inhibitory activity toward NNK
metabolism than PEITC counterparts. In the tumor bioassay, as
expected, the conjugates exhibited inhibitory activity against
lung tumorigenesis induced by NNK. PEITC-GSH was not
inhibitory at 4 µmol/mouse, but it inhibited .apprx.32% of lung
tumor multiplicity at 8 µmol/mouse. PEITC- NAC at 5
and 20 µmol/mouse both inhibited .apprx.30% tumor
multiplicity. Among all the conjugates examined, PHITC-NAC was
the most potent. At a 5-µmol dose, it completely inhibited
tumor multiplicity and incidence to the background level observed in
the control group. These results revealed that the structure-activity
relationships of the conjugates are similar to those found with their
parent isothiocyanates (ITCs), i.e., the potency increased with
the increasing alkyl chain length from two to six carbons in arylalkyl
ITCs, suggesting that a common active species is involved. The inhibitory
activity of ITC conjugates and the expected low toxicity make thiol
conjugates of ITC a promising new series of chemopreventive agents.
OS.CITING REF COUNT: 49 THERE ARE 49 CAPLUS RECORDS THAT CITE THIS
RECORD (49 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1996:747991 CAPLUS
DOCUMENT NUMBER: 126:98839
ORIGINAL REFERENCE NO.: 126:18913a,18916a
TITLE: Inhibition of rat liver cytochrome of P450 isoenzymes
by isothiocyanates and their conjugates: a
structure-activity relationship study
AUTHOR(S): Conaway, C. Clifford; Jiao, Ding; Chung, Fung-Lung
CORPORATE SOURCE: Division of Carcinogenesis and Molecular Epidemiology,
American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Carcinogenesis (1996), 17(11), 2423-2427
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of arylalkyl and alkyl isothiocyanates, and their glutathione, cysteine, and N-acetylcysteine conjugates were used to study their inhibitory activity toward the dealkylation of ethoxyresorufin (EROD), pentoxyresorufin (PROD), and methoxyresorufin (MROD) in liver microsomes obtained from the 3-methylcholanthrene or phenobarbital-treated rats. These reactions are predominantly mediated by cytochrome P 450 (P 450) isoenzymes 1A1 and 1A2, 2B1 and 1A2, resp. All isothiocyanates inhibited PROD more readily than EROD. Increases in the alkyl chain length of arylalkyl isothiocyanates to C6 resulted in an increased inhibitory potency in these assays; at longer alkyl chain lengths (C8-C130) the inhibitory potency declined. The IC50s for phenethyl isothiocyanate (PEITC) were 47, 46 and 1.8 μ M for EROD, MROD and PROD, resp. Substitution of an addnl. Ph group on PEITC also increased the inhibitory potency; the IC50s for 1,2-diphenylethyl isothiocyanate (1,2-DPEITC) and 2,2-diphenylethyl isothiocyanate (2,2-DPEITC) were 0.9 and 0.26 μ M for EROD, and 0.045 and 0.13 μ M for PROD, resp. The relative inhibitory potency of PEITC and its conjugates was N-acetylcysteine-PEITC (PEITC-NAC) < glutathione-PEITC (PEITC-GSH) < cysteine-PEITC (PEITC-CYS) < PEITC. The observations that the parent isothiocyanates were more potent inhibitors than the conjugates suggest that dissociation of the conjugate is required for activity. Naturally occurring alkyl isothiocyanates, sulforaphane (SFO) and allyl isothiocyanate (AITC), were very weak inhibitors in the assays. These results suggest the potential of isothiocyanates as structural probes for studying P 450 isoenzymes. In addition, the inhibitory activity of isothiocyanates for PROD correlated with the previously demonstrated tumor inhibitory potency in (4-methylnitrosamino)-1-(3-pyridyl)-1-butannone (NNK) induced A/J mouse lung tumor bioassays, which supports earlier findings that P 450 2B1 is one of the major isoenzymes involved in NNK activation and that inhibition of this isoenzyme is an important mechanism for the chemopreventive activity of isothiocyanates.

OS.CITING REF COUNT: 69 THERE ARE 69 CAPLUS RECORDS THAT CITE THIS RECORD (69 CITINGS)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 1996:104627 CAPLUS

DOCUMENT NUMBER: 124:193641

ORIGINAL REFERENCE NO.: 124:35515a,35518a

TITLE: Chemopreventive efficacy of arylalkyl isothiocyanates and N-acetylcysteine for lung tumorigenesis in Fischer rats

AUTHOR(S): Chung, Fung-Lung; Kelloff, Gary; Steele, Vernon; Pittman, Brian; Zang, Edith; Jiao, Ding; Rigotty, Jeffrey; Choi, Chang-In; Rivenson, Abraham

CORPORATE SOURCE: Div. Carcinogenesis Mol. Epidemiol., American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595, USA

SOURCE: Cancer Research (1996), 56(4), 772-8
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study is to evaluate the efficacy of three promising sulfur-containing compds., 6-phenylhexyl isothiocyanate (PHITC), phenethyl isothiocyanate (PEITC), and N-acetylcysteine (NAC), as chemopreventive agents in a long-term bioassay for lung tumorigenesis in F34 rats. PEITC occurs as a

constituent of certain cruciferous vegetables, PHITC is a synthetic homolog, and NAC is an endogenous substance. Male F344 rats were treated with the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) by s.c. injection at a dose of 1.5 mg/kg body weight three times weekly for 20 wk. This dose regimen induced a 67% tumor incidence in the lung, a major target organ of NNK. PHITC or PEITC administered in the diet for 22 wk, a period covering from 1 wk before to 1 wk after the NNK treatment, exhibited significant inhibition of lung tumorigenesis induced by NNK. The lung tumor incidences in the NNK-treated groups, fed a diet containing 4 mmol/kg (876 ppm) or 2 mmol/kg (438 ppm) PHITC, were 24 and 19% and were 9 and 17% in groups fed PEITC at concns. of 8 mmol/kg (1304 ppm) or 4 mmol/kg (652 ppm), resp. In contrast to isothiocyanates, NAC given in the diet at 80 mmol/kg (13056 ppm) or 40 mmol/kg (6528 ppm) exerted no inhibitory effects on the NNK-induced lung tumorigenesis. At the dose studied, NNK did not induce liver and pancreatic tumors in the treated animals, but a significant increase of nasal cavity tumor incidence was observed in the NNK-treated group. However, none of the test compds. showed any effect on the tumorigenesis in this tissue. This study demonstrated that PHITC and PEITC were potent chemopreventive agents for the NNK-induced lung tumorigenesis in F344 rats, whereas NAC was not active at all. These results support further evaluation of these compds. in chemoprevention studies.

OS.CITING REF COUNT: 67 THERE ARE 67 CAPLUS RECORDS THAT CITE THIS RECORD (67 CITINGS)

L3 ANSWER 11 OF 16 MEDLINE on STN
 ACCESSION NUMBER: 1996192304 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 8634661
 TITLE: Effects of watercress consumption on metabolism of a tobacco-specific lung carcinogen in smokers.
 AUTHOR: Hecht S S; Chung F L; Richie J P Jr; Akerkar S A; Borukhova A; Skowronski L; Carmella S G
 CORPORATE SOURCE: American Health Foundation, Valhalla, New York 10595, USA.
 CONTRACT NUMBER: CA-46535 (United States NCI NIH HHS)
 SOURCE: Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, (1995 Dec) Vol. 4, No. 8, pp. 877-84. Journal code: 9200608. ISSN: 1055-9965. L-ISSN: 1055-9965.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199607
 ENTRY DATE: Entered STN: 19 Jul 1996
 Last Updated on STN: 19 Jul 1996
 Entered Medline: 10 Jul 1996

AB Epidemiological studies indicate that vegetable consumption protects against lung cancer in humans, but the protective constituents have not been identified. Phenethyl isothiocyanate (PEITC), which is release upon chewing of watercress (nasturtium officinale), is a chemopreventive agent against lung cancer induced by the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in rats and mice. PEITC inhibits the carcinogenicity of NNK by inhibiting its metabolic activation and thereby increasing the levels of detoxified metabolites excreted in urine. In this study, our goal was to determine whether watercress consumption would modify NNK metabolism in smokers. Eleven smokers maintained constant smoking habits and avoided cruciferous

vegetables and other sources of isothiocyanates throughout the study. They donated 24-h urine samples on 3 consecutive days (baseline period). One to 3 days later, they consumed 2 ounces (56.8 g) of watercress at each meal for 3 days and donated 24-h urine samples on each of these days (watercress consumption period). One and 2 weeks later, they again donated 24-h urine samples on 2-3 consecutive days (follow-up periods). The samples were analyzed for two metabolites of NNK; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and [4-methylnitrosamino)-1-(3-pyridyl)but-1-yl]-beta-omega-D-glucosiduro nic acid (NNAL-Gluc). NNAL-Gluc is believed to be a detoxification product of NNK. The urine samples were also analyzed for PEITC-NAC, a metabolite of PEITC. Minimum exposure to PEITC during the watercress consumption period averaged 19-38 mg/day. Seven of the 11 subjects had increased levels of urinary NNAL plus NNAL-Gluc on days 2 and 3 of the watercress consumption period, compared to the baseline period. Overall, the increase in urinary NNAL plus NNAL-Gluc in this period was significant [mean +/- SD 0.924 +/- 1.12 nmol/24 h (33.5%); P < 0.01]. Urinary levels of NNAL plus NNAL-Gluc returned to near baseline levels in the follow-up periods. The percentage of increase in urinary NNAL plus NNAL-Gluc during days 2 and 3 of the watercress consumption period correlated with intake of PEITC during this period, as measured by total urinary PEITC-NAC (r = 0.62; P = 0.04). The results of this study support our hypothesis that PEITC inhibits this oxidative metabolism of NNK in humans, as seen in rodents, and support further development of PEITC as a chemopreventive agent against lung cancer. This is the first study to report an effect of vegetable consumption on metabolism of a lung carcinogen in humans.

L3 ANSWER 12 OF 16 MEDLINE on STN
 ACCESSION NUMBER: 1993290258 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 8512247
 TITLE: Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis by compounds derived from cruciferous vegetables and green tea.
 AUTHOR: Chung F L; Morse M A; Eklind K I; Xu Y
 CORPORATE SOURCE: Division of Chemical Carcinogenesis American Health Foundation, Valhalla, New York 10595.
 CONTRACT NUMBER: CA-46535 (United States NCI NIH HHS)
 CA-51830 (United States NCI NIH HHS)
 SOURCE: Annals of the New York Academy of Sciences, (1993 May 28) Vol. 686, pp. 186-201; discussion 201-2. Ref: 39
 Journal code: 7506858. ISSN: 0077-8923. L-ISSN: 0077-8923.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199307
 ENTRY DATE: Entered STN: 23 Jul 1993
 Last Updated on STN: 23 Jul 1993
 Entered Medline: 15 Jul 1993

AB We have shown that PEITC and I3C, both of cruciferous origin, inhibited lung tumor formation induced by the tobacco-specific nitrosamine NNK. The inhibition by PEITC is due largely to its inhibitory effect on the enzymes of NNK metabolism, whereas; the inhibition by I3C may be attributed to its ability to induce hepatic enzyme activity of NNK metabolism, which resulted in decreased availability of NNK to the lung. On a molar basis, PEITC is considerably more effective than I3C. PEITC was released upon consumption of watercress. The N-acetylcysteine conjugate of PEITC is a promising urinary marker for quantitating uptake of this dietary anticarcinogen in humans. These

studies also showed that green tea polyphenol EGCG inhibited the NNK-induced lung tumorigenesis, probably due to its antioxidant property. These studies provide for the first time evidence for the involvement of free radicals in nitrosamine tumorigenesis. The mechanism by which free radicals are generated by NNK treatment is not yet known. The reduced levels of oxidative lesions in lung as a result of EGCG treatment may be related to its ability to reduce reactive oxygen species and/or to chelate iron ion resulting in a decreased production of hydroxyl radicals. Overall, these studies have identified ingredients in cruciferous vegetables and green tea that are inhibitory against lung tumorigenesis induced by NNK in rodents.

L3 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:439817 CAPLUS

DOCUMENT NUMBER: 117:39817

ORIGINAL REFERENCE NO.: 117:6838h,6839a

TITLE: New potential chemopreventive agents for lung carcinogenesis of tobacco-specific nitrosamine
AUTHOR(S): Chung, Fung Lung; Morse, Mark A.; Eklind, Karin I.
CORPORATE SOURCE: American Health Found., Valhalla, NY, 10595, USA
SOURCE: Cancer Research (1992), 52(9, Suppl.), 2719s-2722s
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cigarette smoking is the major cause of lung cancer in humans. The continuous increase in the prevalence of cigarette smoking worldwide demands a practical means to circumvent this serious health problem. The authors research has focused on the development of new chemopreventive agents against lung carcinogenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Several aromatic isothiocyanates have been identified as effective inhibitors of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Phenethyl isothiocyanate, a natural constituent of cruciferous vegetables, protects F344 rats and A/J mice from 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. The alkyl chain length in the aromatic isothiocyanates is an important structural feature for the inhibitory potency. The inhibitory efficacy increases as the alkyl chain elongates up to 6 carbon atoms. Thus, 6-phenylhexyl isothiocyanate is approx. 50 to 100 times more potent than phenethyl isothiocyanate. The remarkable efficiency of 6-phenylhexyl isothiocyanate suggests its potential as a chemopreventive agent in intervention trials. The tissue distribution and excretion of phenethyl isothiocyanate were studied in mice. Two major urinary metabolites were identified as the mercaptopyruvic acid and the N-acetylcysteine conjugates. A urinary marker was developed to quantitate the uptake of phenethyl isothiocyanate in humans after consumption of watercress, a cruciferous vegetable rich in gluconasturtiin, the glucosinolate precursor of phenethyl isothiocyanate. Considering the anticarcinogenic activity of phenethyl isothiocyanate, this marker may eventually be useful in assessing the role of dietary phenethyl isothiocyanate uptake in lung cancer risk.

OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)

L3 ANSWER 14 OF 16 MEDLINE on STN

ACCESSION NUMBER: 1992224178 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1563003

TITLE: New potential chemopreventive agents for lung

carcinogenesis of tobacco-specific nitrosamine.
AUTHOR: Chung F L; Morse M A; Eklind K I
CORPORATE SOURCE: American Health Foundation, Valhalla, New York 10595.
CONTRACT NUMBER: CA-32272 (United States NCI NIH HHS)
CA-41544 (United States NCI NIH HHS)
CA-46535 (United States NCI NIH HHS)
SOURCE: Cancer research, (1992 May 1) Vol. 52, No. 9 Suppl, pp.
2719s-2722s.
Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 7 Jun 1992
Last Updated on STN: 7 Jun 1992
Entered Medline: 21 May 1992

AB Cigarette smoking is the major cause of lung cancer in humans. The continuous increase in the prevalence of cigarette smoking worldwide demands a practical means to circumvent this serious health problem. Our research has focused on the development of new chemopreventive agents against lung carcinogenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Several aromatic isothiocyanates have been identified as effective inhibitors of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Phenethyl isothiocyanate, a natural constituent of cruciferous vegetables, protects F344 rats and A/J mice from 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. The alkyl chain length in the aromatic isothiocyanates is an important structural feature for the inhibitory potency. The inhibitory efficacy increases as the alkyl chain elongates up to 6 carbon atoms. Thus, 6-phenylhexyl isothiocyanate is approximately 50 to 100 times more potent than phenethyl isothiocyanate. The remarkable efficiency of 6-phenylhexyl isothiocyanate suggests its potential as a chemopreventive agent in intervention trials. The tissue distribution and excretion of phenethyl isothiocyanate were studied in mice. Two major urinary metabolites were identified as the mercaptopyruvic acid and the N-acetylcysteine conjugates. A urinary marker was developed to quantitate the uptake of phenethyl isothiocyanate in humans after consumption of watercress, a cruciferous vegetable rich in glucanasturtiin, the glucosinolate precursor of phenethyl isothiocyanate. Considering the anticarcinogenic activity of phenethyl isothiocyanate, this marker may eventually be useful in assessing the role of dietary phenethyl isothiocyanate uptake in lung cancer risk.

L3 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1994:293485 CAPLUS
DOCUMENT NUMBER: 120:293485
ORIGINAL REFERENCE NO.: 120:51579a,51582a
TITLE: Quantitation of human uptake of the anticarcinogen
phenethyl isothiocyanate after a watercress
meal
AUTHOR(S): Chung, F. L.; Morse, M. A.; Eklind, K. I.; Lewis, J.
CORPORATE SOURCE: Div. Chem. Carcinog., Am. Health Found., Valhalla, NY,
10595, USA
SOURCE: Cancer Epidemiology, Biomarkers & Prevention (1992),
1(5), 383-8
CODEN: CEBPE4; ISSN: 1055-9965

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Phenethyl isothiocyanate (PEITC), a cruciferous vegetable constituent, inhibits the lung tumorigenesis induced by a potent tobacco-specific carcinogenic nitrosamine in animals. These results implicate dietary PEITC as a risk-reducing factor of lung cancers induced by smoking. To define the effect of dietary PEITC on human cancers, a method of measuring its uptake is needed. Since watercress is rich in gluconasturtiin, a glucosinolate precursor of PEITC, it was chosen to be the source of PEITC. Four individuals were asked to eat watercress as part of a breakfast meal, and 24-h urine samples were collected. A urinary metabolite was found, and its identity was confirmed as the N-acetylcysteine conjugate of PEITC by comparison with the synthetic standard using NMR and mass spectrometry. A dose-dependent excretion of this conjugate was observed. These results clearly showed that PEITC was released in the human body upon ingestion of watercress and suggest that the N-acetylcysteine conjugate of PEITC may be a useful marker for quantitating human exposure to this anticarcinogen as a tool for epidemiol. investigations.

OS.CITING REF COUNT: 112 THERE ARE 112 CAPLUS RECORDS THAT CITE THIS RECORD (113 CITINGS)

L3 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 1991:76760 CAPLUS

DOCUMENT NUMBER: 114:76760

ORIGINAL REFERENCE NO.: 114:12983a,12986a

TITLE: Distribution and metabolism of the natural anticarcinogen phenethyl isothiocyanate in A/J mice

AUTHOR(S): Eklind, Karin I.; Morse, Mark A.; Chung, Fung Lung

CORPORATE SOURCE: Div. Chem. Carcinog., American Health Found., Valhalla, NY, 10595, USA

SOURCE: Carcinogenesis (1990), 11(11), 2033-6
CODEN: CRNGDP; ISSN: 0143-3334

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The distribution and metabolism of phenethyl isothiocyanate (PEITC), a naturally occurring anticarcinogen, was investigated in A/J mice. Mice were administered 5 μ mol of [14C]PEITC (2 μ Ci/mouse) by gavage and killed at 1, 2, 4, 8, 24, 48, or 72 h after dosing. Radioactivity present in the spleen, heart, liver, lung, kidney, brain, urine, and feces was measured. Lung, the target tissue of PEITC inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) lung tumorigenesis, showed maximum radioactivity between 4 and 8 h after dosing, suggesting this time period would be optimal for maximal inhibition by PEITC in A/J mice. Approx. 50% of the total radioactivity was excreted within 24 h after dosing with nearly 80% of radioactivity found in urine and feces at 72 h. Two metabolites were isolated by reversed-phase HPLC from urine of mice treated with PEITC. The identities of these metabolites were determined by comparison with synthetic stds. and by NMR and MS. The major metabolite was a cyclic mercaptopyruvic acid conjugate, whereas the minor metabolite was an N-acetylcysteine conjugate. Approx. 25% of the administered dose of PEITC was excreted as the cyclic mercaptopyruvic acid conjugate and 10% as the N-acetylcysteine conjugate. These results suggest that urinary metabolites of PEITC may provide potentially useful dosimeters for this natural anticarcinogen.

OS.CITING REF COUNT: 41 THERE ARE 41 CAPLUS RECORDS THAT CITE THIS RECORD (41 CITINGS)

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